

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-138

20-164 S-075

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



sanofi aventis

Because health matters

300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Patent Information and Certification

Form FDA 3542a for the following patent is included:

United States Patent No. RE 38,743E

**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 20-164/S- |
| NAME OF APPLICANT / NDA HOLDER Sanofi-aventis U.S. LLC |

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

TRADE NAME (OR PROPOSED TRADE NAME)
Lovenox®

| | |
|---|--|
| ACTIVE INGREDIENT(S) Enoxaparin Sodium | STRENGTH(S) 30 mg/0.3 mL pre-filled syringes; 40 mg/0.4 mL pre-filled syringes; 60 mg/0.6 mL graduated pre-filled syringes; 80 mg/0.8 mL graduated pre-filled syringes; 100 mg/1.0 mL graduated pre-filled syringes; 90 mg/0.6 mL graduated pre-filled syringes; 120 mg/0.8 mL graduated pre-filled syringes; 150 mg/1.0 mL graduated pre-filled syringes; 30 mg/0.3 mL ampoules; 300 mg/3.0 mL Multiple-Dose Vials |
|---|--|

DOSAGE FORM
Injection

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

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

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

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

1. GENERAL

| | | |
|---|--------------------------------------|---|
| a. United States Patent Number RE 38,743 E | b. Issue Date of Patent 6/14/2005 | c. Expiration Date of Patent 2/14/2012 |
|---|--------------------------------------|---|

| | | |
|--|---|--|
| d. Name of Patent Owner Aventis Pharma S.A. | Address (of Patent Owner) 20 avenue Raymond Aron | |
| | City/State 92165 Antony | |
| | ZIP Code France | FAX Number (if available) 011 33 1 557 16524 |
| | Telephone Number 011 331 557 16892 | E-Mail Address (if available) Gerald.Dahling@sanofi-aventis.com |

| | | |
|--|--|--|
| 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) Carolyn D. Moon | Address (of agent or representative named in 1.e.) Sanofi-Aventis, 1041 Route 202-206, Box 6800 | |
| | City/State Bridgewater, NJ | |
| | ZIP Code 08807 | FAX Number (if available) 908-231-2840 |
| | Telephone Number 908-231-2356 | E-Mail Address (if available) carolyn.moon@sanofi-aventis.com |

| | | |
|--|---|--|
| f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? | <input checked="" type="checkbox"/> Yes | <input type="checkbox"/> No |
| g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? | <input type="checkbox"/> Yes | <input checked="" type="checkbox"/> 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 **Not Applicable**

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. Not applicable because 2.3 was not applicable in view of the fact that the answer to 2.2 was no

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 24, 25, 26, and 29 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) See attached sheet

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 **Not Applicable**

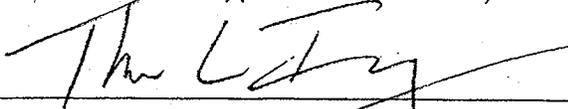
6. Declaration Certification

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



November 6, 2006

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
Thomas L. Irving

Address
901 New York Avenue

City/State
Washington, D.C

ZIP Code
20001-4413

Telephone Number
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FAX Number (if available)
202 408 4400

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The public reporting burden for this collection of information has been estimated to average 9 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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahim/fdahim.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

NDA Holder: Sanofi-aventis U.S. LLC

RE 38,743

Additional Pages for Patent Information Submitted Upon and After Approval of an NDA or Supplement

1.e. Not applicable because NDA Holder, sanofi-aventis U.S. LLC, resides and/or has a place of business within the United States. However, this information is nonetheless provided.

2.1: Note, e.g., claim 1.

2.3. No need to answer since answer to 2.2 is no.

2.7: It is not considered correct to characterize the patent as a product-by-process patent to the extent that other non-product-by-process claims, such as "a heterogeneous intimate admixture of sulfated heparinic polysaccharides" (claim 1), are set forth in the patent. At least claim 32 is, however, an active ingredient product-by-process claim, and the active ingredient recited therein is considered novel. Hence, it is concluded that the correct answer to question 2.7 is yes, but that answer is in no way an admission that the patent contains only product-by-process claims.

3.1: Note, e.g., claim 30. Drug product as defined in 21 CFR 314.3 means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. Claim 30 does not recite tablet, capsule, or solution, but recites a therapeutic composition of matter for defined purpose comprising a defined heterogeneous polysaccharide admixture and a therapeutically acceptable carrier or diluent therefore. As a legal matter, claim 30 would read on any finished dosage form, for example, tablets, capsules, or solutions, that comprise the heterogeneous polysaccharide admixture defined in claim 30 and a therapeutically acceptable carrier or diluent therefore. It is, therefore, believed that the correct answer to 3.1 is yes.

3.3: As explained in the answer to 2.7, it is not believed correct to characterize the patent as a product-by-process patent to the extent that other non-product-by-process claims, such as "a heterogeneous intimate admixture of sulfated heparinic polysaccharides" (claim 1), are set forth in the patent. In any event, it is not believed that any product-by-process claim in the patent relates to a drug product-by-process. As noted in 2.7, however, at least claim 32 is an active ingredient product-by-process claim, and the active ingredient recited therein is considered novel. Hence, in view of at least claim 32, it was considered appropriate to check yes as the answer for 3.3.

4.1: The patent contains method of use claims 24, 25, 26, and 29. The proposed Lovenox prescribing information being submitted to the FDA with the filing of the subject supplemental NDA for enoxaparin in the treatment of patients with acute ST-segment elevation myocardial infarction, including patients to be managed medically or with

NDA Holder: Sanofi-aventis U.S. LLC

RE 38,743

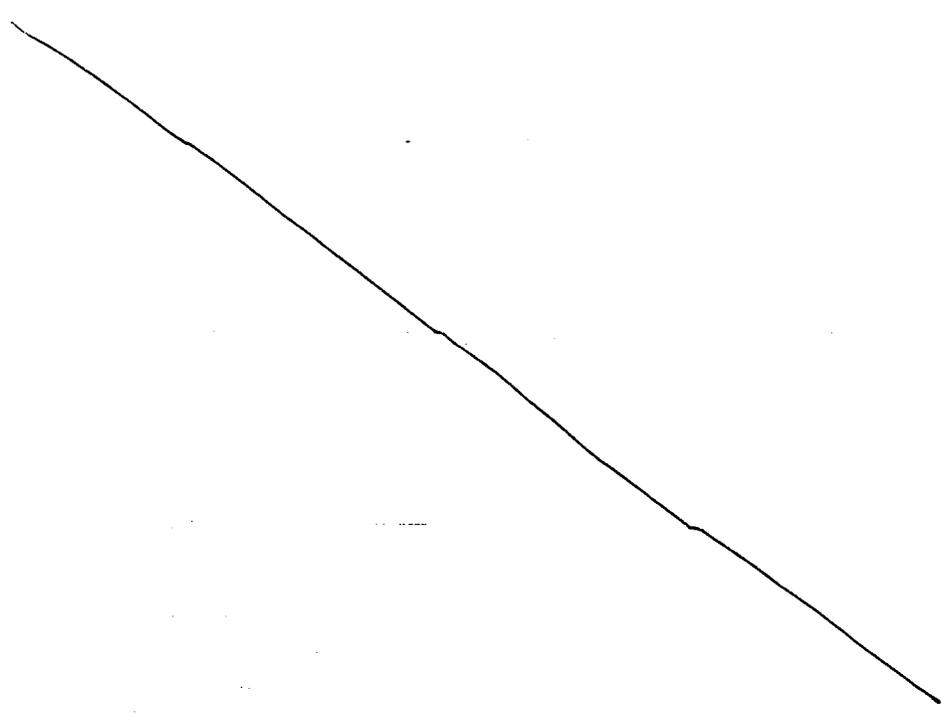
subsequent Percutaneous Coronary Intervention (PCI) (hereafter, "Lovenox Proposed USPI"), is based on the findings provided in certain final study reports relating to such methods of use, as explained further below. In addition, method of use approval was obtained in the original NDA. Further, 21 CFR 314.53 (c) states: "For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use that are described in the pending or approved application." Therefore, it is believed appropriate to answer yes to 4.1.

4.2: In view of the information recited above in 4.1, it is believed appropriate to answer yes to 4.2.

4.2a. The following information sets forth each of claims 24, 25, 26, and 29, with applicable approved label extracts from the Lovenox Proposed USPI set forth for each claim.

- **Claim 24: A method for the prevention of thrombotic episodes in a human patient, comprising administering to a human in need of such prevention, a therapeutically effective amount of the heterogeneous polysaccharide admixture as defined by claim 1.**

Label Excerpts:



b(4)

4 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative-1

EXCLUSIVITY SUMMARY

NDA # 22-138

SUPPL # 000

HFD # 110

Trade Name Lovenox

Generic Name enoxaparin sodium

Applicant Name Sanofi-Aventis

Approval Date, If Known May 16, 2007

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

SE-1 - new indication for ST-segment elevation myocardial infarction

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?

3 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# 20-164

Lovenox (enoxaparin sodium)

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:

ExTRACT Study

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

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

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

Investigation #1

YES

NO

Investigation #2

YES

NO

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

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

Investigation #1

YES

NO

Investigation #2

YES

NO

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

Not Applicable

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

Not Applicable

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

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

Investigation #1
IND # 31,532 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

Not Applicable

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Meg Pease-Fye, M.S.

Title: Regulatory Health Project Manager

Date: May 17, 2007

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

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/

Margaret Pease-Fye

5/30/2007 03:17:54 PM

This revised exclusivity checklist replaces the one signed on
May 18, 2007. The question under Part III,
3A should have been "no" instead of "yes."
The question asks if the study was relied
upon for another drug. This was a new
study.

Norman Stockbridge

5/30/2007 06:00:36 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-138 Supplement Type: SE-1 Supplement Number: 000

Stamp Date: November 17, 2006 PDUFA Goal Date: May 17, 2007

HFD 110 Trade and generic names/dosage form: Lovenox (enoxaparm sodium) injection

Applicant: Sanofi-Aventis Therapeutic Class: low molecular weight heparins

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

Yes. Please proceed to the next question.

Indication(s) previously approved (please complete this section for supplements only):

- Prophylaxis of deep vein thrombosis
- Treatment of Acute Deep Vein Thrombosis
- Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-wave Myocardial Infarction

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: acute ST-Segment Elevation Myocardial Infarction (STEMI) in the labeling.

Is this an orphan indication?

No. Please proceed to the next question.

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

Yes: Please proceed to Section A.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Disease/condition is rare in children

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

This page was completed by:

{See appended electronic signature page}

Meg Pease-Fye, M.S.
Regulatory Project Manager

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

/s/

Margaret Pease-Fye
5/23/2007 01:12:51 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 31,532

RECEIVED JUL 24 2006

sanofi-aventis, U.S. Inc.
Attention: Eddie Li, Ph.D.
Regulatory Development Project Leader
Director of Regulatory Affairs
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your submission dated May 23, 2006, requesting a waiver for pediatric studies for Lovenox[®] (enoxaparin sodium, Injection).

We have reviewed the submission and agree that a waiver is justified for Lovenox[®] (enoxaparin sodium, injection) for the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI) for the entire pediatric population because that condition is rare in children.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, contact Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

George Q. Mills, M.D., M.B.A.
Director
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

George Mills
7/19/2006 08:35:55 AM

**sanofi aventis**

Because health matters

23 May 2006

George Q. Mills, M.D., Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Subject: IND 31,532; Lovenox® (enoxaparin sodium) Injection; RP 54563
Serial No. 0860
Request for Pediatric Waiver**

Dear Dr. Mills:

Reference is made to the subject IND and the upcoming supplement to Lovenox NDA 20-164, to be indicated for the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI). Reference is also made to 21 CFR 314.55, and the draft guidance document "Recommendations for Complying With the Pediatric Rule [21 CFR 314.55(a) and 601.27(a)]."

As of 01 April 1999, all applications for new active ingredients are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Further, as of 02 December 2000, required assessments of pediatric safety and effectiveness must be submitted with an application, unless the assessments are waived or deferred by FDA.

Age groups

In compliance with the 63 FR 66670 and in accordance with the draft guidance, the Sponsor is submitting a request for a full waiver (all pediatric age groups) of the pediatric study requirements as specified in 21 CFR 314.55(c) for enoxaparin in the indication of ST-segment elevation acute myocardial infarction.

Regulatory Criteria For Waiving Pediatric Studies

Under the criteria provided in the pediatric rule, a waiver will be granted if the waiver request demonstrates that the product meets both the following conditions: (1) The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments, and (2) the product is not likely to be used in a substantial number of pediatric patients. FDA has developed a list of diseases that have extremely limited applicability to pediatric patients and for which products under development in adults are likely to be granted a pediatric waiver. Such conditions include arteriosclerosis.

Justification for the Enoxaparin Pediatric Waiver for the Indication of ST-Segment Elevation Acute Myocardial Infarction

Substantial Number of Pediatric Patients

As defined in 63 FR 66670, the cut-off for a substantial number of pediatric patients is 50,000 pediatric patients with the disease or condition for which the drug is indicated.

The most recent data taken from the 2003 National Hospital Discharge Survey (NHDS; July 8, 2005) provided no data for patients under the age of 15 for acute myocardial infarction, coronary atherosclerosis or other ischemic heart disease, but only a footnote indicating that such data do not meet standards of reliability or precision (ie, fewer than 30 records in the sample or a relative standard error >30%.) The actual values are quite small, as data are reported for incidence rates as low as 1.2 per 10,000 (cardiac dysrhythmia). Therefore, it can be concluded that the number of pediatric patients with ST-elevation acute myocardial infarction is even smaller and well below the 50,000 patient cut-off.

Meaningful Therapeutic Benefit

The rare pediatric patients with atherosclerosis (and the potential for acute MI) as described above are currently treated with HMG-CoA reductase inhibitors to lower lipid levels in response to the underlying etiology of their disease. Enoxaparin's known mechanism of action does not support a meaningful therapeutic benefit on this basis and such a comparison would be unreasonable. Additionally, due to the constraints of the extremely limited numbers of potential patients as described above, no meaningful data could be obtained.

The Sponsor, therefore, concludes that adequate evidence has been provided to satisfy conditions cited for waiving pediatric studies and that a full waiver of the pediatric assessment requirement for upcoming Acute MI supplement to NDA 20-164 is justified.

Sanofi-aventis U.S. Inc. understands that this IND and all information contained therein, unless otherwise made public by sanofi-aventis U.S. Inc., is confidential.

If you have any questions or comments, please do not hesitate to contact me by telephone (610-889-6554) or by email (eddie.li@sanofi-aventis.com), or in my absence, Jon Villaume, Ph.D. at 610-889-6028.

Sincerely,

for E. Li

Eddie Li, Ph.D.
Regulatory Development Project Leader
Director of Regulatory Affairs
Sanofi-aventis U.S. Inc.
11 Great Valley Parkway
Malvern, PA 19355



sanofi aventis

Because health matters

Debarment Certification

June 5, 2006

Sanofi-aventis U.S. LLC hereby certifies that it has not used and will not use in any capacity the services of any person debarred pursuant to section 306(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 335(a) and (b)] in connection with this application.

A handwritten signature in black ink, appearing to read "Eddie Li", written over a horizontal line.

Eddie Li, Ph.D.
Regulatory Development Project Leader
Director of Regulatory Affairs
sanofi-aventis U.S. Inc.
on behalf of sanofi-aventis U.S. LLC
11 Great Valley Parkway
Malvern, PA 19355

Financial Disclosure

Dr. U addressed the Financial Disclosure statement on pages 27 by saying the following in his review dated March 28, 2007:

“This submission consists of one pivotal, phase III study, XRP4563B/3001 (ExTRACT TIMI-25), in support of the use of enoxaparin in the treatment of patients with STEMI.

In compliance with 21 CFR Part 54 and the March 20, 2001 FDA Guidance, “Financial Disclosure by Clinical Investigators”, the sponsor provided a list of principle investigators participating in the ExTRACT study, and submitted certification that all of the principle investigators who participated in the ExTRACT study declared that they had no financial interests in the outcome of the study.”

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| | | |
|------------------------|--|--|
| Clinical Investigators | See attached list of investigators with no financial interests in outcome of study ExTRACT | |
| | | |
| | | |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| | |
|--|--|
| NAME Eddie Li, Ph.D. | TITLE Regulatory Development Project Leader Director of Regulatory Affairs Sanofi-aventis U.S. Inc. on behalf of snaofi-aventis U.S. LLC |
| FIRM / ORGANIZATION snaofi-aventis U.S. LLC | |
| SIGNATURE | DATE 6/5/06 |

An agency **NDA 20164 Supplement** a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

financial.pdf - 002
Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DRM FDA 3454 (4/06)

PSC Graphics: (301) 443-1090 EF

Financial Disclosure Information

This submission consists of one pivotal, phase III study, XRP4563B/3001 (ExTRACT TIMI-25), in support of the use of Lovenox (enoxaparin) in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI). In compliance with 21 CFR Part 54 and the March 20, 2001 FDA Guidance, "Financial Disclosure by Clinical Investigators", financial disclosure information is provided in this section for ExTRACT. Included in this section are the following items:

- Form FDA 3453
- List of all the principle investigators participating in ExTRACT who have declared that they have no financial interests in the outcome of the study.

Zhang, Sherry PH/US

From: Foldes, Csilla PH/US
sent: Tuesday, October 24, 2006 10:01 AM
To: Li, Eddie Sanofi; Zhang, Sherry PH/US; Gural, Richard Sanofi; Cumiskey, Wayne Sanofi
Cc: Parker, James A (USRA) PH/US
Subject: Lovenox STEMI sNDA Wire Transfer - Completed

The Lovenox STEMI sNDA application user fee payment of US \$ 448,100.00 has been wired to the FDA for sNDA 20-164.

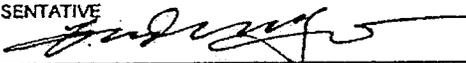
Below is a "visual capture" copy available from the wire transfer system - in case you want to retain with your FDA files. Please note the new format of the wire transfer due to new system capture reporting.

Please share this information with others within CRA as needed.

Best regards,
Csilla

Csilla Földes, M.S.
Director, Regulatory Submissions
US RAMP - Medical Affairs
sanofi-aventis U.S. Inc.
300 Somerset Corporate Blvd.
Bridgewater, NJ 08807-0977
Mail Stop: SC3-615A
ph: 908-243-7438
fx: 908-243-6017
cell: 908-510-4755
mail: csilla.foldes@sanofi-aventis.com

b(4)

| | | |
|---|--|--|
| Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See Instructions for OMB Statement | | |
| 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 Shery Zhang 300 Somerset Corporate Blvd Bridgewater NJ 08807 US | | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 20-164 |
| 2. TELEPHONE NUMBER 908-231-3275 | | 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 Lovenox (Enoxaparin Sodium) | | 6. USER FEE I.D. NUMBER PD3006809 |
| 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 | | |
| 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: 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 Dir., Reg Affairs DATE Nov. 17, 2006 |
| 9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$448,100.00 | | |
| Form FDA 3397 (12/03) | | |

(IBE_PRMT_CLOSE_G) (Print Cover sheet)

| | | | | | |
|-------------|--|---------|--------------|---------|------|
| | DBA GLAXOSMITHKLINE | 3006781 | N020241 | 448,100 | CDER |
| 13-NOV-2006 | SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE | 3006782 | N022115 | 896,200 | CDER |
| 09-NOV-2006 | ASTRAZENECA LP | 3006828 | N022056 | 896,200 | CDER |
| 09-NOV-2006 | MEDPOINTE HEALTHCARE INC | 3006819 | N011792 | 448,100 | CDER |
| 08-NOV-2006 | GENZYME CORP | 3006817 | 103661 | 383,700 | CBER |
| 07-NOV-2006 | DAIICHI SANKYO INC | 3006796 | NDA022100 | 896,200 | CDER |
| 03-NOV-2006 | AMGEN INC | 3006834 | 103951/5137 | 448,100 | CDER |
| 02-NOV-2006 | ABBOTT LABORATORIES | 3006827 | 125057 | 448,100 | CDER |
| 01-NOV-2006 | OMRIX BIOPHARMACEUTICALS LTD | 3006771 | BLA | 896,199 | CBER |
| 01-NOV-2006 | GLAXOSMITHKLINE | 10575 | N021036 | 142,870 | CDER |
| 01-NOV-2006 | ELI LILLY AND CO | 3006826 | N021427 | 448,100 | CDER |
| 31-OCT-2006 | ELI LILLY AND CO | 3006805 | N020592 | 448,100 | CDER |
| 31-OCT-2006 | ELI LILLY AND CO | 3006806 | N020592 | 448,100 | CDER |
| 25-OCT-2006 | AMYLIN PHARMACEUTICALS INC | 3006807 | N021332 | 448,100 | CDER |
| 23-OCT-2006 | SANOFI AVENTIS US LLC | 3006809 | N020164 | 448,100 | CDER |
| 13-OCT-2006 | INDEVUS PHARMACEUTICALS INC | 3006775 | N022103 | 896,200 | CDER |
| 11-OCT-2006 | SOLVAY PHARMACEUTICALS INC | 3006780 | N022077 | 896,200 | CDER |
| 10-OCT-2006 | LIFECYCLE PHARMA AS | 3006773 | N022118 | 896,200 | CDER |
| 06-OCT-2006 | SANOFI PASTEUR | 3006755 | BLA 125244/0 | 448,100 | CBER |
| 05-OCT-2006 | NOVARTIS PHARMACEUTICALS | | | | |



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164

Sanofi-Aventis U.S. Inc.
Attention: Eddie Li, Ph. D.
Director, Regulatory Affairs
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your new drug application (NDA) for Lovenox[®] (enoxaparin sodium, injection).

We also refer to the package insert approved in Supplemental New Drug Application (S-075) submitted on November 17, 2006 (received November 17, 2006) and approved May 16, 2007. This application proposed labeling for a new indication of acute ST-Segment Elevation myocardial Infarction (STEMI).

Upon further review of the labeling approved in S-075, we have determined that several aspects of the label should be revised to improve readability and consistency with the content and format specified by 21 CFR 201.56 and associated guidance documents (available at <http://www.fda.gov/cder/regulatory/physLabel/default.htm>). We request that you submit a prior approval supplement to this application which incorporates the changes in the attached labeling so as to furnish adequate information for the safe and effective use of the drug.

We are enclosing a clean copy and a marked-up copy for your convenience. In the marked-up version, deletions are denoted with strikeouts. Additions are denoted with double underlines.

In addition to the revisions highlighted in the attachment, please include the following:

1. In Section **6 ADVERSE REACTIONS**, please fill in the proper patient numbers and check the dose ranges.
2. In Section **8.1 Pregnancy**, please explain why this is a category B drug.
3. In section **14.6 Treatment of acute ST-Segment Elevation Myocardial Infarction**, please insert a clearer chart under Figure 1 entitled "**Relative Risks of and Absolute Event Rates for the Primary End Point at 30 Days in Various Subgroups.**"

4. In section **14.6 Treatment of acute ST-Segment Elevation Myocardial Infarction**, please insert a clearer figure for Figure 2 entitled “Kaplan-Meier plot - death or myocardial re-infarction at 30 days - ITT population.”
5. Please note in the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, that the section headings do not contain a line space before the text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of the **HIGHLIGHTS OF PRESCRIBING INFORMATION**. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

In addition, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that incorporates the revisions from the enclosed labeling (text for the package insert).

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Acting Director
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachments:

PI Marked-up Copy
PI Clean Copy

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

/s/

Rafel Rieves

7/18/2007 03:51:19 PM



NDA 22-138

DISCIPLINE REVIEW LETTER

Sanofi-Aventis U.S. Inc.
Attention: Eddie Li, Ph. D.
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your November 17, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium).

We also refer to your submissions dated December 20, 2006, January 8 and 12, February 1, 9, 21, and 28, March 12, 13, 16, 19 and 23, and May 2, 2007.

Our review of the Clinical Pharmacology section of your submission is complete, and we have identified the following deficiencies:

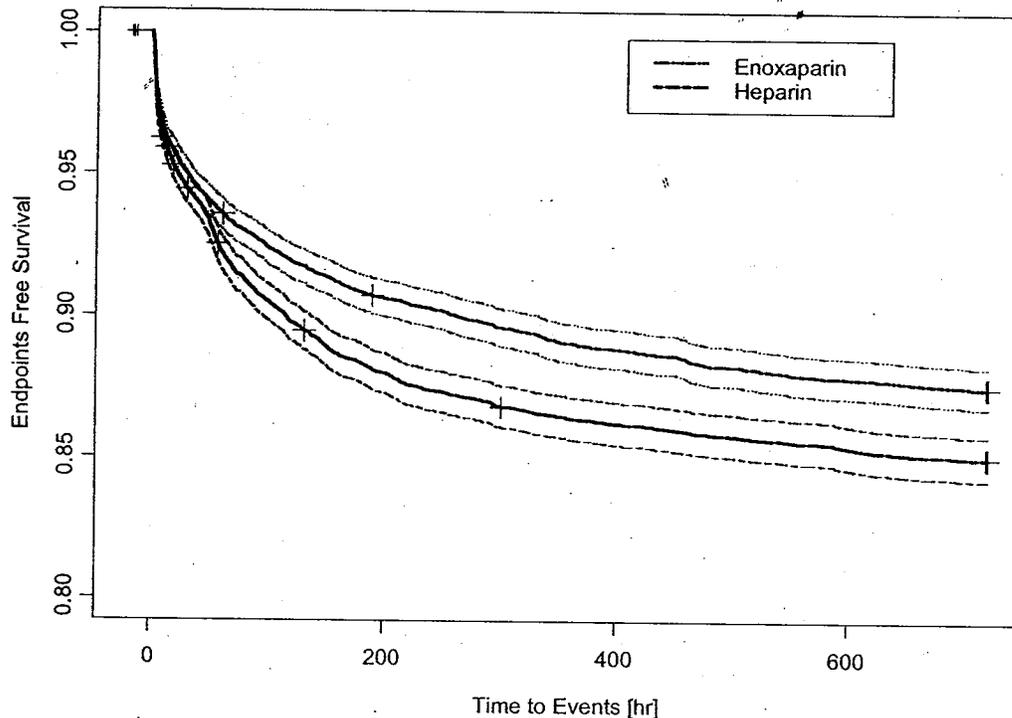
- Although mortality was part of the composite primary end point and it trended reasonably in favor of enoxaparin ($p=0.11$ at 30 days), differences in location of the index MIs (more anterior infarcts in the heparin group) further undermine the interpretability of this finding. Please analyze mortality based on the site of infarction (any anterior versus other sites of infarction).

TIMI-25 study used unfractionated heparin (UFH) as a control. Heparin is not approved for this indication; however, ACC guidelines support use of this regimen, but it has only class C evidentiary support (consensus opinion of experts; no supportive randomized trials). We investigated the effectiveness of heparin for this indication as well as whether treatment duration is important for the enoxaparin arm by using the Cox proportional hazard with a time dependent treatment effect approach. The pharmacometric group at OCP of FDA conducted the following analysis.

- **Compared to heparin, does enoxaparin provide any benefit for the time to major events (death, or MI) up to 30 days?**

The time to major events (death or MI) following enoxaparin or UFH treatment was demonstrated in Figure 1. Non-parametric (log-rank) analysis showed statistically significant ($P < 0.0001$) benefit of time to major events for enoxaparin compared to heparin treatment. The mean time to events was 648 (± 2.23) and 631 (± 2.45) hours for enoxaparin and heparin treated group respectively.

Figure 1 Kaplan-Meier Plot (with 95% Confidence Intervals) for Time to Major Events (Death, MI or Urgent Revascularization) Up to 30 Days

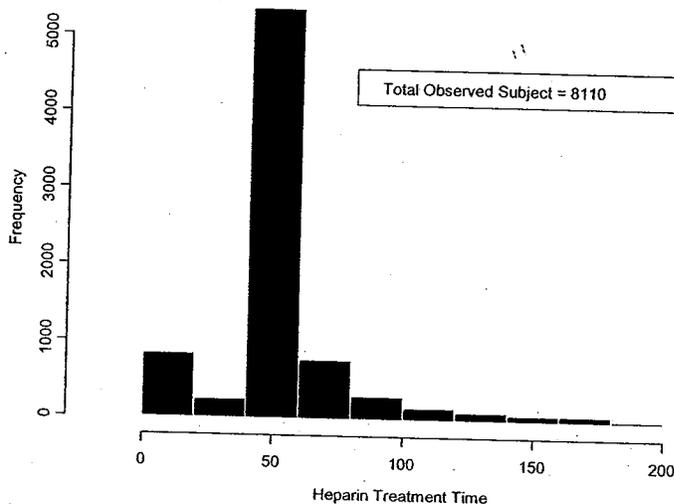


- **Is UFH effective? If so, is the UFH dose used in the study TIMI-25 optimal?**
TIMI-25 study used UFH as a control. All subjects in the TIMI-25 study received 150 mg to 325 mg of non-enteric coated acetylsalicylic acid (ASA) orally (chewed) or 500 mg intravenously as soon as they were identified with STEMI. Maintenance ASA therapy was administered at a dose of 75 to 325 mg once daily (coated or uncoated) for a minimum of 30 days unless contraindications applied. Each subject received only 1 permitted fibrinolytic drug, administered according to its approved label. Subjects randomized to UFH group received an initial iv bolus of 60 U/kg (maximum 4000 U), and within 15 minutes a continuous iv infusion was to be started at 12 U/kg (maximum 1000 U/hour initially). Intravenous UFH was to continue for a minimum of 48 hours or until percutaneous coronary intervention (PCI).

To answer a question about effectiveness, two groups are typically compared (*e.g.* heparin versus placebo or active control). Since the primary variable of interest is the time to event for the heparin arm, it is most appropriate to analyze these data using Cox Proportional Hazard analysis with UFH treatment as time dependant variable, limited to the cohort of patients randomized to UFH.

In total, 10,223 patients were employed in the heparin treated group. Patients with no record of treatment (censoring indicator) were excluded from analysis. As demonstrated in Figure 2, 8110 patients were included in the analysis; the median heparin duration time was 48 hours, and all patients stopped heparin treatment within 8-9 days.

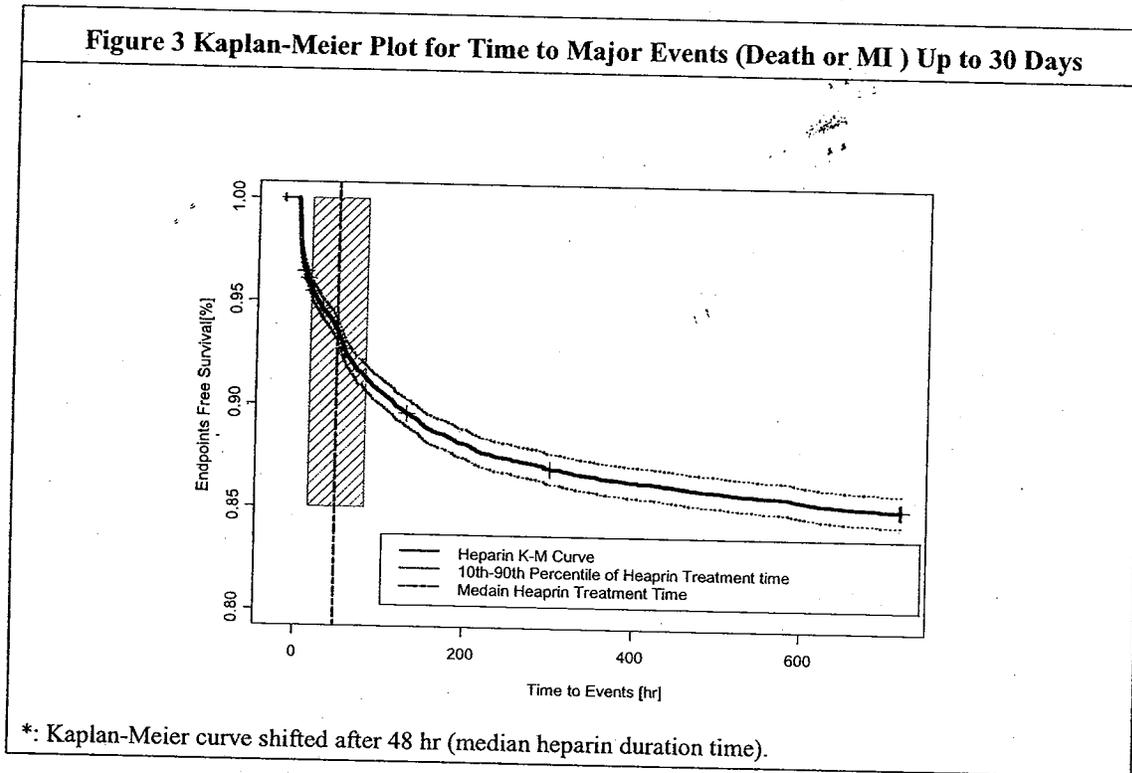
Figure 2 Heparin Duration Time Distribution in TIMI-25 Study



*: Median Heparin Duration Time = 48 hr.

APPEARS THIS WAY ON ORIGINAL

Event free survival time curve is presented in Figure 3: Kaplan-Meier Plot for Time to Major Events (Death or MI) Up to 30 days.



APPEARS THIS WAY ON ORIGINAL

The Kaplan-Meier curve shifted after 48 hours (the median heparin duration time). A life-table hazard function for the heparin treated group is presented in Figure 4.

Semi-parametric survival analysis (Cox Proportional hazard model) using heparin treatment as time-dependant variable was employed for data analysis. In this analysis, the treatment variable is assigned as "0" when the time is less than heparin duration time, otherwise it is assigned as "1" for each individual. Every individual will have some "ones" and some "zeroes." Therefore, heparin duration time for each individual is included in the analysis. The results are listed in Table 1, which indicate that heparin treatment significantly reduces hazard of major events of interest ($P < 0.0001$).

Figure 4. Life-table Hazard Function vs. Time for Heparin Treatment Arm.
 (x-axis is time in hours and y-axis is hazard of the event occurrence)

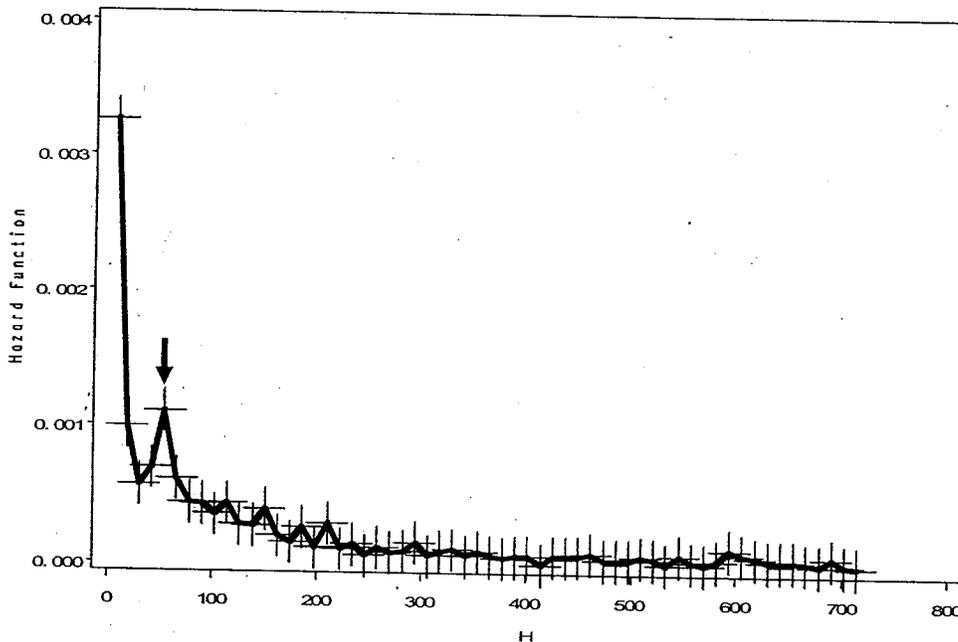


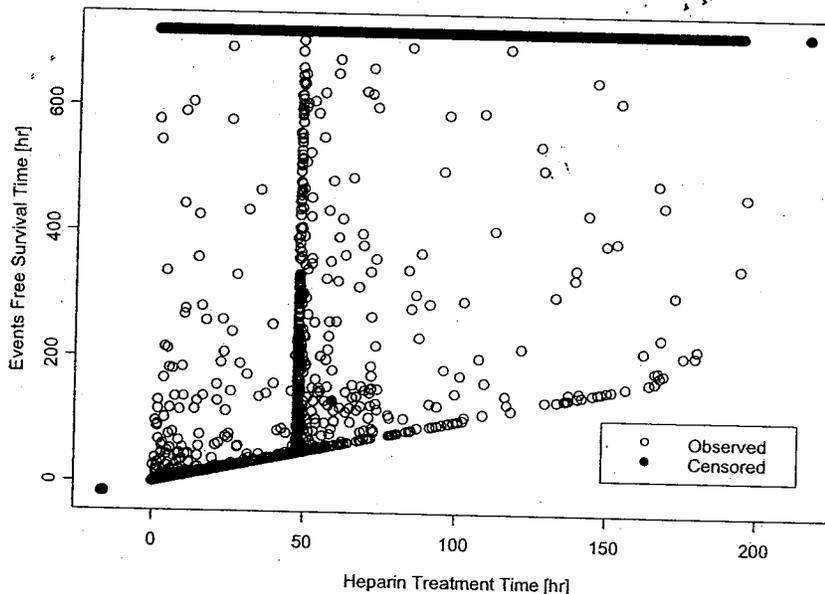
Table 1 Cox Proportional Hazard Analysis using Heparin Treatment as Time Dependant Variable

| Parameter Estimates | Standard Error | Chi-square | P | Hazard Ratio |
|---------------------|----------------|------------|---------|--------------|
| 3.43 | 0.09 | 1360.24 | <0.0001 | 31.02 |

The relationship between observed or censored event time and heparin duration time was plotted in Figure 5. A linear pattern could be identified for some of the data, indicating the patients who had events (such as death) early and thus did not receive any further heparin treatment. Therefore, the heparin duration time and event free survival time are two confounded factors

from some of the patients *i.e.*, a patient merely staying in the trial (event-free) is associated with a finite but higher probability of receiving heparin treatment longer.

Figure 5 Plot of Heparin Duration Time versus Observed or Censored Events Time



A sensitivity analysis was conducted using subsets of data with different heparin duration times to explore the benefit of heparin treatment with different duration time. The following is the value of such sensitivity analyses (internal consistency). If most of the 'significance' for the heparin effect is derived from those patients who did not have events, and got heparin longer, then excluding such patients with extreme heparin duration times will diminish the significance. Subsets of data with heparin duration times less than or equal to 82.7, 48.08, and 16.8 hours (corresponding to 90th, 50th, and 10th percentile of the heparin duration time in the TIMI-25 trial) respectively were employed in the Cox Proportional Hazard analysis using heparin treatment as time-dependant variable. It is important to note that patients were excluded for these sensitivity analyses based on heparin treatment duration and NOT based on the time of the major event they might have had.

The results are listed in Table 2. Statistically significant ($P < 0.0001$) heparin treatment effect can be demonstrated for the time to major events for all the subsets. Although, subjects with short heparin treatment duration time of ≤ 16.8 hours were usually high-risk patients and tended to have early events, the hazard of events for an average subject increased about 3-fold when the heparin treatment was discontinued. Inclusion of subjects with longer heparin duration time (≤ 48.08 or 82.7 hours) also meant that more heparin responders (or less risky subjects) were included for analysis. Discontinuation of heparin treatment in this patient population yielded higher hazard ratio (25 to 32 fold) for

time to major events compared to patients who discontinued heparin ≤ 16.8 hours. The outcome further demonstrated that heparin is effective for this indication.

Table 2 Cox Proportional Hazard Analysis using Heparin Treatment as Time Dependent Variable (Subsets of Data with Heparin Duration Time not Greater Than 82.7, 48.08, and 16.8 hr [Correspondent to 90th, 50th, 10th Percentile of Heparin Duration Time in the TIMI-25 Study])

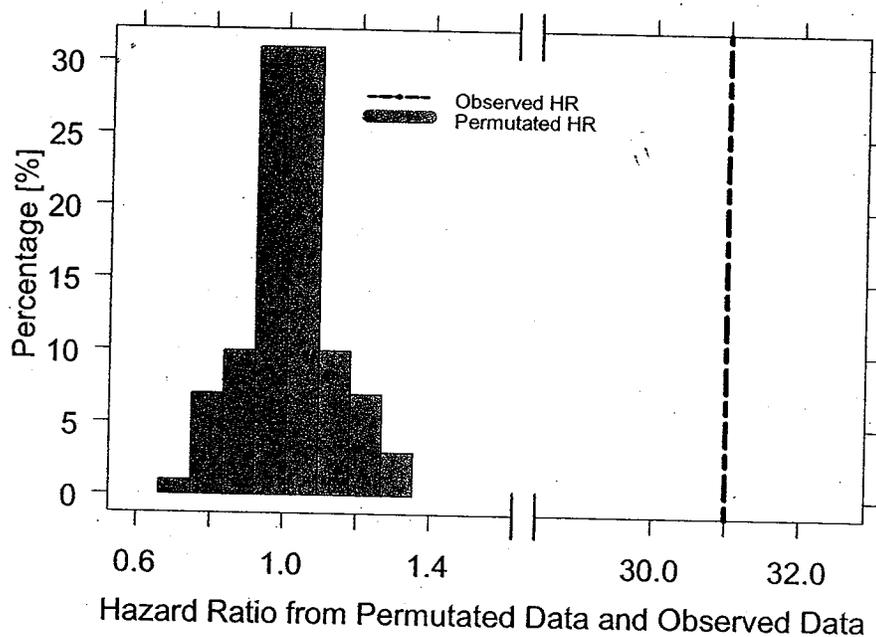
| Data Set | Parameter Estimate | Standard Error | Chi-square | P | Hazard Ratio |
|-------------------------------|--------------------|----------------|------------|---------|--------------|
| Duration Time ≤ 82.7 hr | 3.49 | 0.095 | 1356.28 | <0.0001 | 32.69 |
| Duration Time ≤ 48.08 hr | 3.23 | 0.1 | 1038.09 | <0.0001 | 25.27 |
| Duration Time ≤ 16.8 hr | 1.22 | 0.13 | 89.25 | <0.0001 | 3.4 |

In order to further address the question whether the treatment effect demonstrated in the Cox Proportional Hazard Model was a coincident time effect from the disease progression, a permutation test was conducted. The heparin duration time and the event time relationship was randomly permuted 100 times (*i.e.*, 100 permuted data sets were created), whereas the heparin event time (together with the event type) was preserved. Since the permutations perturb the relationship, if any, between event time and heparin duration time (null model) the heparin treatment duration should be found significant only for a nominal number of cases ($\sim 5\%$ at an alpha of 5%). Further, the hazard ratio (HR) should be centered at 1 for these permuted data sets, much removed from the observed HR of 31. The results from the permutation test are summarized below:

1. The outcome from permutation test is presented in Table A1 in Appendix. Out of 100 permuted datasets, only 7 demonstrated significant treatment effect. Among them, 4 with the hazard ratio were significantly lower than 1. That is, the nominal alpha is $\sim 4\%$.
2. The hazard ratio from the observed data and the permuted data was presented in Figure 6. The hazard ratio values, for the permuted data sets, are close to 1 and the observed hazard ratio from the Cox Proportional Hazard analysis is 31, which is far above any values seen in the permuted datasets. The results indicate that the observed heparin treatment effect and the hazard ratio are not purely by chance or entirely driven by natural disease progression.

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Figure 6 Hazard ratio from observed and permuted dataset



UFH was administered as continuous iv infusion in the TIMI-25 study for about 48 hours for most patients. The major shift in the event free survival curve [Figure 3 Kaplan-Meier Plot for Time to Major Events (Death or MI) Up to 30 Days] suggested that if a patient tolerates heparin treatment, longer heparin treatment (longer than 48 hours) is beneficial. Results from the Cox Proportional Hazard analysis with time dependant treatment variable also inferred that longer heparin duration time yields lower risk; however, the optimal duration of heparin treatment is still yet to be determined.

- **Is enoxaparin treatment duration an important prognostic factor of hazard of MI/death?**

The same Cox proportional hazard model with time dependent treatment variables were employed for enoxaparin datasets, for additional validation of the conclusions about heparin treatment effect. The treatment variable is assigned as "0" when the time is less than enoxaparin duration time, otherwise it is assigned as "1" for each individual. Even though the Kaplan-Meier curve looks smooth for enoxaparin treatment group (Figure 7), the statistical significant treatment effect was also demonstrated with $P < 0.0001$. The calculated hazard ratio is 54.21 (Table 3), further supporting that treatment duration is important. Within the tested treatment duration range, to be on enoxaparin treatment is always beneficial compared to being off treatment, which indicates that longer enoxaparin treatment might be

also beneficial in reducing the event risk; however, the optimal enoxaparin treatment duration is still yet to be determined, considering the natural disease progression and the risk of adverse events.

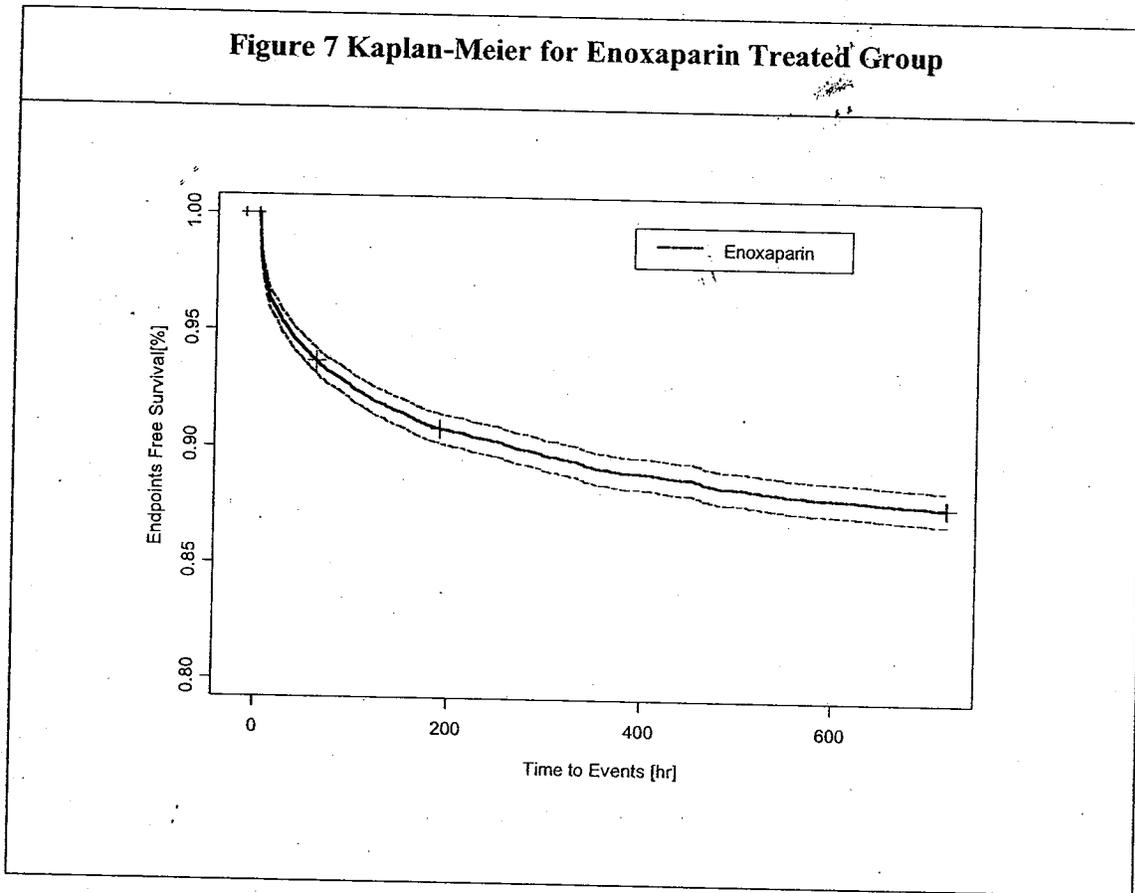


Table 3 Cox Proportional Hazard Analysis using Enoxaparin Treatment as Time Dependant Variable

| Parameter Estimates | Standard Error | Chi-square | P | Hazard Ratio |
|---------------------|----------------|------------|---------|--------------|
| 3.99 | 0.107 | 1396.7 | <0.0001 | 54.21 |

Based on the finding from above analyses, FDA believes that:

1. Compared to heparin, enoxaparin treatment for the time to major events (death, myocardial infarction) up to 30 days was found to be significant ($p < 0.0001$). More importantly, the mean survival times for enoxaparin and heparin are 648 (± 2.23) and 631 (± 2.45) hours.
2. Based on the UFH-arm data collected from Study TIMI-25, UFH is effective for the treatment of patients with STEMI. Specifically, patients who stopped heparin had 31-

- fold higher hazard ratio of death or MI than those who were on heparin. This shows heparin is effective in reducing the hazard of one or more of the major events of interest.
3. Longer duration time is beneficial, for both enoxaparin and heparin, in reducing the hazard of events (death or MI); however, the optimal dosing regimen for both drugs is unknown at this point.
 4. The UFH was administered as an initial iv bolus of 60 U/kg (maximum 4000 U), and within 15 minutes a continuous iv infusion was started at 12 U/kg (maximum 1000 U/hour initially). For most patients, the UFH was continued for a median of 48 hr (16.8 – 82.7 hour of the 10th and 90th duration time) or until events occurred. Optimal dosing regimen still needs to be determined.

This document is provided to you as background material and may be followed by a teleconference to discuss the next steps. We will be more than glad to clarify any technical details before the teleconference if necessary.

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:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

Sincerely,

{See appended electronic signature page}

Abraham Karkowsky, M.D., Ph.D.
Acting Deputy Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

appendix

Table A1. Permutation Outcomes

| RUN | Convergence | Parameter | SE | Chi-square | P | Hazard Ratio |
|-----|-------------|-----------|---------|------------|--------|--------------|
| 1 | S | -0.04288 | 0.11557 | 0.1376 | 0.7106 | 0.958 |
| 2 | S | 0.14271 | 0.11499 | 1.5404 | 0.2146 | 1.153 |
| 3 | S | 0.08287 | 0.11487 | 0.5204 | 0.4707 | 1.086 |
| 4 | S | 0.072 | 0.11522 | 0.3905 | 0.532 | 1.075 |
| 5 | S | 0.1644 | 0.11464 | 2.0564 | 0.1516 | 1.179 |
| 6 | S | -0.21502 | 0.11548 | 3.4669 | 0.0626 | 0.807 |
| 7 | S | 0.07628 | 0.11471 | 0.4422 | 0.5061 | 1.079 |
| 8 | S | 0 | 0.11551 | 0 | 1 | 1 |
| 9 | S | -0.10967 | 0.11525 | 0.9054 | 0.3413 | 0.896 |
| 10 | S | 0.02181 | 0.11526 | 0.0358 | 0.8499 | 1.022 |
| 11 | S | -0.40366 | 0.11532 | 12.2522 | 0.0005 | 0.668 |
| 12 | S | -0.17346 | 0.11541 | 2.2588 | 0.1329 | 0.841 |
| 13 | S | 0.03324 | 0.11529 | 0.0831 | 0.7731 | 1.034 |
| 14 | S | -0.25571 | 0.11551 | 4.9009 | 0.0268 | 0.774 |
| 15 | S | -0.04985 | 0.11528 | 0.187 | 0.6654 | 0.951 |
| 16 | S | 0.22455 | 0.11455 | 3.8429 | 0.05 | 1.252 |
| 17 | S | 0.03436 | 0.11546 | 0.0885 | 0.766 | 1.035 |
| 18 | S | 0.25908 | 0.11386 | 5.1779 | 0.0229 | 1.296 |
| 19 | S | 0.13408 | 0.11492 | 1.3612 | 0.2433 | 1.143 |
| 20 | S | -0.00432 | 0.11521 | 0.0014 | 0.9701 | 0.996 |
| 21 | S | -0.02789 | 0.11519 | 0.0586 | 0.8087 | 0.972 |
| 22 | S | -0.09486 | 0.11496 | 0.6808 | 0.4093 | 0.91 |
| 23 | S | 0.06945 | 0.11523 | 0.3632 | 0.5467 | 1.072 |
| 24 | S | 0.16731 | 0.11426 | 2.1441 | 0.1431 | 1.182 |
| 25 | S | -0.06172 | 0.11515 | 0.2873 | 0.592 | 0.94 |
| 26 | S | 0.03679 | 0.11517 | 0.102 | 0.7494 | 1.037 |
| 27 | S | -0.03742 | 0.11529 | 0.1054 | 0.7455 | 0.963 |
| 28 | S | -0.04972 | 0.11513 | 0.1865 | 0.6659 | 0.952 |
| 29 | S | -0.00457 | 0.11534 | 0.0016 | 0.9684 | 0.995 |
| 30 | S | -0.00349 | 0.11522 | 0.0009 | 0.9758 | 0.997 |
| 31 | S | 0.08379 | 0.11487 | 0.5321 | 0.4657 | 1.087 |
| 32 | S | 0.0739 | 0.11508 | 0.4124 | 0.5207 | 1.077 |
| 33 | S | -0.07351 | 0.11554 | 0.4048 | 0.5246 | 0.929 |
| 34 | S | 0.05101 | 0.11517 | 0.1962 | 0.6578 | 1.052 |
| 35 | S | 0.10646 | 0.11511 | 0.8553 | 0.355 | 1.112 |
| 36 | S | 0.03106 | 0.11508 | 0.0729 | 0.7872 | 1.032 |
| 37 | S | 0.00268 | 0.11528 | 0.0005 | 0.9815 | 1.003 |
| 38 | S | -0.11646 | 0.11611 | 1.0059 | 0.3159 | 0.89 |
| 39 | S | 0.0998 | 0.11518 | 0.7508 | 0.3862 | 1.105 |
| 40 | S | 0.09591 | 0.1153 | 0.6919 | 0.4055 | 1.101 |
| 41 | S | 0.05835 | 0.11525 | 0.2563 | 0.6127 | 1.06 |
| 42 | S | -0.06686 | 0.11513 | 0.3373 | 0.5614 | 0.935 |

| | | | | | | |
|----|---|----------|---------|--------|--------|-------|
| 43 | S | -0.06045 | 0.11558 | 0.2735 | 0.601 | 0.941 |
| 44 | S | -0.07125 | 0.11538 | 0.3813 | 0.5369 | 0.931 |
| 45 | S | 0.06241 | 0.115 | 0.2945 | 0.5874 | 1.064 |
| 46 | S | 0.03318 | 0.11551 | 0.0825 | 0.7739 | 1.034 |
| 47 | S | 0.09167 | 0.11514 | 0.6339 | 0.4259 | 1.096 |
| 48 | S | 0.11539 | 0.11521 | 1.0032 | 0.3165 | 1.122 |
| 49 | S | -0.04436 | 0.11548 | 0.1476 | 0.7008 | 0.957 |
| 50 | S | 0 | 0.11562 | 0 | 1 | 1 |
| 51 | S | -0.19997 | 0.1157 | 2.9872 | 0.0839 | 0.819 |
| 52 | S | 0.04443 | 0.11497 | 0.1494 | 0.6992 | 1.045 |
| 53 | S | -0.22578 | 0.1151 | 3.8478 | 0.0498 | 0.798 |
| 54 | S | -0.02665 | 0.11546 | 0.0533 | 0.8175 | 0.974 |
| 55 | S | -0.08029 | 0.11553 | 0.4829 | 0.4871 | 0.923 |
| 56 | S | -0.0457 | 0.11521 | 0.1573 | 0.6916 | 0.955 |
| 57 | S | 0.07818 | 0.11536 | 0.4592 | 0.498 | 1.081 |
| 58 | S | 0.29764 | 0.1139 | 6.8284 | 0.009 | 1.347 |
| 59 | S | -0.06811 | 0.11534 | 0.3487 | 0.5548 | 0.934 |
| 60 | S | -0.07161 | 0.11537 | 0.3852 | 0.5348 | 0.931 |
| 61 | S | -0.04326 | 0.11553 | 0.1402 | 0.7081 | 0.958 |
| 62 | S | 0.03766 | 0.11538 | 0.1065 | 0.7442 | 1.038 |
| 63 | S | 0.16784 | 0.1148 | 2.1376 | 0.1437 | 1.183 |
| 64 | S | 0.04155 | 0.11484 | 0.1309 | 0.7175 | 1.042 |
| 65 | S | 0.07902 | 0.11476 | 0.4741 | 0.4911 | 1.082 |
| 66 | S | 0.19477 | 0.11453 | 2.8923 | 0.089 | 1.215 |
| 67 | S | 0.06235 | 0.11494 | 0.2943 | 0.5875 | 1.064 |
| 68 | S | 0.03596 | 0.11492 | 0.0979 | 0.7543 | 1.037 |
| 69 | S | 0.06178 | 0.11513 | 0.288 | 0.5915 | 1.064 |
| 70 | S | -0.17399 | 0.11535 | 2.2753 | 0.1314 | 0.84 |
| 71 | S | -0.16139 | 0.11558 | 1.9498 | 0.1626 | 0.851 |
| 72 | S | -0.18689 | 0.11516 | 2.634 | 0.1046 | 0.83 |
| 73 | S | 0.01585 | 0.11547 | 0.0189 | 0.8908 | 1.016 |
| 74 | S | -0.15563 | 0.11505 | 1.8298 | 0.1762 | 0.856 |
| 75 | S | 0.16691 | 0.11451 | 2.1248 | 0.1449 | 1.182 |
| 76 | S | -0.02583 | 0.11505 | 0.0504 | 0.8224 | 0.975 |
| 77 | S | 0.19285 | 0.11454 | 2.8348 | 0.0922 | 1.213 |
| 78 | S | 0.01596 | 0.11526 | 0.0192 | 0.8899 | 1.016 |
| 79 | S | -0.00131 | 0.11538 | 0.0001 | 0.991 | 0.999 |
| 80 | S | 0.09355 | 0.115 | 0.6618 | 0.4159 | 1.098 |
| 81 | S | -0.13323 | 0.11546 | 1.3316 | 0.2485 | 0.875 |
| 82 | S | -0.00266 | 0.11524 | 0.0005 | 0.9816 | 0.997 |
| 83 | S | 0.07752 | 0.1153 | 0.4521 | 0.5014 | 1.081 |
| 84 | S | -0.21422 | 0.11528 | 3.453 | 0.0631 | 0.807 |
| 85 | S | 0.16746 | 0.1147 | 2.1313 | 0.1443 | 1.182 |
| 86 | S | -0.16257 | 0.11552 | 1.9805 | 0.1593 | 0.85 |
| 87 | S | 0.06844 | 0.11505 | 0.3539 | 0.5519 | 1.071 |
| 88 | S | 0.00844 | 0.11498 | 0.0054 | 0.9415 | 1.008 |
| 89 | S | -0.04385 | 0.11531 | 0.1446 | 0.7037 | 0.957 |
| 90 | S | 0.00248 | 0.1155 | 0.0005 | 0.9829 | 1.002 |
| 91 | S | -0.24984 | 0.11555 | 4.675 | 0.0306 | 0.779 |
| 92 | S | 0.06844 | 0.11512 | 0.3535 | 0.5521 | 1.071 |

| | | | | | | |
|-----|---|----------|---------|--------|--------|-------|
| 93 | S | -0.07629 | 0.11516 | 0.4389 | 0.5077 | 0.927 |
| 94 | S | 0.15515 | 0.11458 | 1.8337 | 0.1757 | 1.168 |
| 95 | S | -0.02939 | 0.11523 | 0.065 | 0.7987 | 0.971 |
| 96 | S | 0.24399 | 0.11442 | 4.5477 | 0.033 | 1.276 |
| 97 | S | -0.05511 | 0.11545 | 0.2279 | 0.6331 | 0.946 |
| 98 | S | 0.07693 | 0.11514 | 0.4464 | 0.504 | 1.08 |
| 99 | S | 0.02049 | 0.11535 | 0.0315 | 0.859 | 1.021 |
| 100 | S | -0.15755 | 0.11554 | 1.8592 | 0.1727 | 0.854 |

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

/s/

Abraham Karkowsky
5/11/2007 12:57:47 PM
For Dr, Norman Stockbridge



NDA 22-138

DISCIPLINE REVIEW LETTER

Sanofi-Aventis U.S. Inc.
Attention: Eddie Li, Ph. D.
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your November 17, 2006 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We also refer to your submissions dated January 12, February 9 and 28, 2007.

Our review of the Clinical and Clinical Pharmacology sections of your submission are near completion, and we have made requests for the following additional information:

Clinical (requested in 74-Day letter sent on January 30, 2007)

- Please provide funnel plots of primary efficacy endpoint events by site, by country, and by region.
- Please provide the primary efficacy endpoint data and analyses by subgroups of
 - (i) presence or absence of severe renal impairment (CrCl <30ml), and
 - (ii) patients with and without intracranial hemorrhage, in a table similar to that in Table 18 (Primary efficacy analysis by subgroup analysis – ITT population) on page 76 of the Clinical Study Report 3001.pdf.
 - (iii) Relationship of TIMI major hemorrhage at 30 days to primary efficacy endpoint events: For patients who experienced a TIMI major hemorrhage at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of patients who reached one of the components of the composite primary efficacy endpoint (you may use the sample tables below or choose any other way to present the data).

Table 1 30-day deaths in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | Deaths in 30 days | | |
|-----------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _d (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 2 30-day non-fatal MI in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | MI in 30 days | | |
|-----------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _m (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_m = number (%) of patients who had non-fatal MKI;
 HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 3 Composite primary efficacy endpoint in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | Composite primary endpoint in 30 days | | |
|-----------------------|-----------------|---|---------------------------------------|-------------|---------|
| | | | N _e (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_e = number (%) of patients who reached primary efficacy endpoint event; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Relationship of intracranial hemorrhage (ICH) at 30 days to primary efficacy endpoint events: For patients who experienced an ICH at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of patients who reached one of the components of the composite primary efficacy endpoint (you may use the sample tables below or choose any other way to present the data).

Table 4 30-day deaths in relation to intracranial hemorrhage at 30 days

| Intracranial hemorrhage | Treatment group | N | Deaths in 30 days | | |
|-------------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _d (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 5 30-day non-fatal MI in relation to intracranial hemorrhage at 30 days

| Intracranial hemorrhage | Treatment group | N | MI in 30 days | | |
|-------------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _m (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |

N = Total number of patients in treatment group; N_m = number (%) of patients who had non-fatal MKI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

| | | | | | | | | | |
|--------------|--|--|--|--|--|--|--|--|--|
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

Table 12 Outcome at 6 and 12 months in patients who experienced a TIMI hemorrhage at 30 days (N=349)

| Type of Event | Total Enox UFH N= 211 N= 138 | Six months follow up | | | | Twelve months follow up | | | |
|---------------|------------------------------------|----------------------|-----------|-------------|---------|-------------------------|-----------|-------------|---------|
| | | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value |
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

Table 13 Outcome at 6 and 12 months in patients who had an intracranial hemorrhage at 30 days (N=150)

| Type of Event | Total Enox UFH N= 84 N= 66 | Six months follow up | | | | Twelve months follow up | | | |
|---------------|----------------------------------|----------------------|-----------|-------------|---------|-------------------------|-----------|-------------|---------|
| | | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value |
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

- Among patients who did NOT experience a primary efficacy endpoint event, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six months (and one year) post randomization (you may use the sample tables below or choose any other way to present the data).

Table 14 One-year deaths among patients who did NOT experience a primary efficacy endpoint event

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|--------------------|-------------|---------|---------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
 N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 15 One-year recurrent MI among patients who did NOT experience a primary efficacy endpoint event

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Among patients who did experienced a TIMI major hemorrhage event at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six-month (or one-year) post randomization. This data may be quite similar to that in Table 12 (you may use the sample tables below or choose any other way to present the data).

Table 16 One-year deaths among patients who experienced a TIMI major hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 17 One-year recurrent MI among patients who experienced a TIMI major hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Among patients who did experienced a TIMI minor hemorrhage event at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six months (or one year) post randomization (you may use the sample tables below or choose any other way to present the data).

| | | | | | | | | | | |
|--------|--|--|--|--|--|--|--|--|--|--|
| Stroke | | | | | | | | | | |
|--------|--|--|--|--|--|--|--|--|--|--|

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

- (you may use the sample tables below or choose any other way to present the data).

Table 20 One-year deaths among patients who experienced an intracranial hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|--------------------|-------------|---------|---------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 21 One-year recurrent MI among patients who experienced an intracranial hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|--------------------|-------------|---------|---------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Clinical Pharmacology (requested in 74-Day letter sent on January 30, 2007)

- The sensitivity of the anti-Xa activity based enoxaparin assay is insufficient for determining apparent $t_{1/2\lambda z}$.
- The sensitivity of the anti-IIa activity based enoxaparin assay is insufficient for determining the time profile during the 12-hour dose interval and as a result the ratio of the anti-Xa activity to the anti-IIa activity during a dose interval is unknown for enoxaparin.
- The therapeutic range of enoxaparin plasma concentrations has been defined considering only the anti-Xa activity. A rationale has not been provided in this submission.
- The relative contributions of the anti-IIa- and anti-Xa-activities to the effect of enoxaparin on aPTT have not been defined in this submission.
- The cross-reactivity of F IIa and F Xa for S2239, and CBS3139, respectively, has not been submitted in this submission.
- The contribution of endogenous mucopolysaccharides to background activity appears not to have been determined in plasma.
- With the anti-Xa activity based assay instability was observed when the samples were exposed to room temperature for ≥ 3 hours. A safe time for exposure of the samples to room temperature was not determined. What was the sample handling in studies RP54563Q-142 and RP54563Q-266?
- A single freeze-thaw cycle affects the precision and accuracy of the anti-Xa activity based assay at the 0.25 IU anti-Xa/mL level (study DMPK/FR/2032). Despite that the plasma concentrations were measured to the lowest level of 0.25 IU anti-Xa /mL in study RP54563Q-142.
- The anti-Xa-activity based assay in urine does not meet the precision and accuracy limits and no stability data are available (study IBP/Biodyn 1772RP54563 Enoxaparin). What was the sample handling in Study RP54563Q-142? Renal clearance and amounts excreted in urine based on the anti-Xa activity have been

reported for enoxaparin in study RP54563Q-142. Information on the impact of endogenous mucopolysaccharides to background activity is also not provided.

- The anti-IIa activity of enoxaparin in urine is impacted by freeze/thaw cycling. What was the sample handling in study RP54563Q-142?

Additional Clinical Pharmacology Information Requested:

- In your answer to the Agency's question 5. Possible cross-reactivity of F IIa and F Xa for CBS3139 and S2238, respectively, you provided 4 figures and 2 tables.

Please provide a more detailed account of how the in vitro experiments were performed.

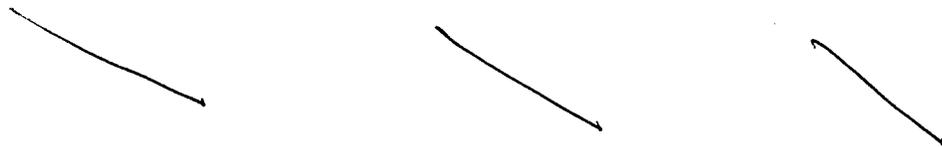
Please send figures with readable symbols on the y- and x- axes.

With respect to F IIa + CBS3139 you state that, "Despite there was a non linear hydrolysis, the delta of the absorbance data of the corresponding enzymatic curves demonstrates a complete loss of sensibility to the presence of enoxaparin. The tabulated values in column "F IIa + CBS3139" indicate that F IIa hydrolyzes CBS3139 completely, implying 0 anti- II activity. Please indicate what you mean by nonlinear hydrolysis and what the anomaly of the curves in Figure b is.

With respect to F Xa + S 2238 you state that the enzymic reaction curve is abnormal. The tabulated values in column "F Xa + S2238" indicate no hydrolysis of S2238 is occurring implying 100 % anti-Xa activity. Please indicate what you mean by abnormal enzymic reaction curve (Figure d).

- In addressing Agency's question 7 you did not provide information on a safe time for samples to be exposed to room temperature. You mention that the samples were kept at 4° before and after analysis. Thus, it appears that sample stability/performance during the assay procedure with exposure to 4° and room temperature is unknown for the anti-Xa based assay. The same problem appears to exist for the anti IIa based assay.
- Study report RP 54563Q-266 states that based on the results of TIMI IIA the therapeutic range of enoxaparin is 0.5 to 1.1 IU anti-Xa activity/mL. Despite this the target range for the anti-Xa activity from 0-2 h after the PCI IV bolus was set to 0.6 -1.8 IU/mL. Please provide a rationale for this discrepancy. Also provide supporting evidence for limiting the first 2 SC administrations to 100 mg. Also, indicate where in the submission supporting evidence can be found for the postulated therapeutic range of enoxaparin. Should this information not be contained in the present submission we request that you provide a copy of the corresponding report and the individual data sets.
- The label for the STEMI indication states that the threshold of 100 mg enoxaparin for the first 2 sc maintenance doses should not be exceeded. Please provide supporting evidence for this dose adjustment.
- Table 7, p. 42 of report RP54563Q-266 compares the possible impact of eptifibatide co-administration on enoxaparin's anti-Xa activities. The tables contain columns entitled "with Integrilin" (eptifibatide) and "without Integrilin and without Reopro" (abciximab). What other co-medications did the respective patient groups have on board? It is unclear how the presence or absence of a drug interaction can be determined if the 2 collects investigated differ possibly in more than the presence/absence of eptifibatide?
- The precision of aPTT that you performed in your laboratories was outside of the upper limits of standards valid in 1989. Have you cross-validated "your aPTT" with an aPTT of a certified laboratory using standards of 2007?
- The data sets you provided contained AUC values in IU *h/mL. Were these AUC0-12h values measured at steady state?

Physician's Labeling Rule Revisions



b(4)

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

b(4)

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

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
3/8/2007 04:49:20 PM

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fml.pdf>)

YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years 3 NO

- Correctly worded Debarment Certification included with authorized signature? YES NO

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers:
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ and preliminary responses sent on _____ NO
April 24, 2006
- Any SPA agreements? Date(s) _____ NO

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to
DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for
scheduling submitted? NA YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **Not Applicable**
YES NO

Chemistry

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

ATTACHMENT
MEMO OF FILING MEETING

DATE: January 10, 2007

NDA #: 22-138

DRUG NAMES: Lovenox (enoxaparin sodium)

APPLICANT: Sanofi Aventis

BACKGROUND:

Lovenox was approved March 29, 1993 for the following indications:

- prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness;
- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin;
- the inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin sodium; and
- the outpatient treatment of acute DVT without PE when administered in conjunction with warfarin sodium.

On August 1, 2006, the Division of Cardiovascular and Renal Products received a Type 6 efficacy supplement for Lovenox containing clinical study data in supporting their proposal for a new indication for ST-segment Elevation Myocardial Infarction (STEMI). Sanofi-Aventis submitted results from a single pivotal clinical study, EXTRACT, and six earlier studies (ASSENT 3, ASSENT 3 Plus, AMI-SK, HART-2, ENTIRE-TIMI-23, and TETAMI). Sanofi believes that Lovenox shows improvement over unfractionated heparin, and requested a priority review. An End of Phase 2 meeting was held with the Division of Gastrointestinal and Coagulation Drug Products on December 14, 2001 and a pre-supplemental NDA meeting was requested with the Division of Medical Imaging and Hematology Products which was cancelled after preliminary responses were sent and accepted.

ATTENDEES:

| | |
|--------------------------------|---|
| Norman Stockbridge, M.D., Ph.D | Director, Division of Cardiovascular and Renal Products |
| Thomas Marciniak, M.D. | Team Leader, Medical Officers |
| Khin U, M.D. | Medical Officer |
| Rajnikanth Madabushi, Ph.D. | Clinical Pharmacology and Biopharmaceutics |
| Edward Fromm, R. Ph. | Chief, Project Management Staff |
| Meg Pease-Fye, M.S. | Regulatory Project Manager |

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

| <u>Discipline/Organization</u> | <u>Reviewer</u> |
|---------------------------------------|------------------------|
| Medical: | Khin U |
| Secondary Medical: | |
| Statistical: | John Lawrence |
| Pharmacology: | Not Applicable |

Statistical Pharmacology: Not Applicable
 Chemistry: Not Applicable
 Environmental Assessment (if needed): Kasturi Srinivasachar
 Biopharmaceutical: Peter Hinderling
 Microbiology, sterility: Not Applicable
 Microbiology, clinical (for antimicrobial products only):
 DSI: Not Applicable
 OPS:
 Regulatory Project Management: Meg Pease-Fye
 Other Consults:

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

There was no site out of the 674 sites (even large sites that enrolled 235 to >300 patients each), where the data are driving the primary efficacy endpoint results of the ExTRACT TIMI-25 trial.

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

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
 N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? YES NO
 • Sterile product? YES NO
 If yes, was microbiology consulted for validation of sterilization?
 YES NO

ELECTRONIC SUBMISSION:
 Any comments:

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

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

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Meg Pease-Fye, M.S.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

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

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

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

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

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
Lovanox (enoxaparin sodium) NDA 20-164

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

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

YES NO

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

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

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

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

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application:

This application provides for a new indication, ST-Segment Elevation Myocardial Infarction

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
 - Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
 - 21 CFR 314.50(i)(1)(ii): No relevant patents.
 - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

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

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|-----------------|-------------|------------------|------------------------|
| | | | |
| | | | |
| | | | |

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

/s/

Margaret Pease-Fye
2/1/2007 01:03:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-138

Sanofi-Aventis U.S. Inc.
Attention: Eddie Li, Ph.D.
Director, Regulatory Affairs
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your November 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We also refer to your submission dated January 19, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 16, 2007 in accordance with 21 CFR 314.101(a).

We are providing the following 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 also request that you submit the following information:

Clinical

- Please provide funnel plots of primary efficacy endpoint events by site, by country, and by region.
- Please provide the primary efficacy endpoint data and analyses by subgroups of
 - (i) presence or absence of severe renal impairment (CrCl <30ml), and
 - (ii) patients with and without intracranial hemorrhage, in a table similar to that in Table 18 (Primary efficacy analysis by subgroup analysis – ITT population) on page 76 of the Clinical Study Report 3001.pdf.
- Relationship of TIMI major hemorrhage at 30 days to primary efficacy endpoint events: For patients who experienced a TIMI major hemorrhage at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of patients who reached one of the components of the composite primary efficacy endpoint (you may use the sample tables below or choose any other way to present the data).

Table 1 30-day deaths in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | Deaths in 30 days | | |
|-----------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _d (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 2 30-day non-fatal MI in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | MI in 30 days | | |
|-----------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _m (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_m = number (%) of patients who had non-fatal MKI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 3 Composite primary efficacy endpoint in relation to a TIMI major hemorrhage at 30 days

| TIMI major hemorrhage | Treatment group | N | Composite primary endpoint in 30 days | | |
|-----------------------|-----------------|---|---------------------------------------|-------------|---------|
| | | | N _e (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_e = number (%) of patients who reached primary efficacy endpoint event; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Relationship of intracranial hemorrhage (ICH) at 30 days to primary efficacy endpoint events: For patients who experienced an ICH at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of patients who reached one of the components of the composite primary efficacy endpoint (you may use the sample tables below or choose any other way to present the data).

Table 4 30-day deaths in relation to intracranial hemorrhage at 30 days

| Intracranial hemorrhage | Treatment group | N | Deaths in 30 days | | |
|-------------------------|-----------------|---|--------------------|-------------|---------|
| | | | N _d (%) | HR 95% C.I. | P value |
| Present | Enoxaparin | | | | |
| | UFH | | | | |
| Absent | Enoxaparin | | | | |
| | UFH | | | | |

N = Total number of patients in treatment group; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

| | | | | | | | | | |
|--------------|--|--|--|--|--|--|--|--|--|
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

Table 11 Outcome at 6 and 12 months follow up in patients who experienced a disabling stroke at 30 days (N=177)

| Type of Event | Total Enoxa UFH N= 87 N= 96 | Six months follow up | | | | Twelve months follow up | | | |
|---------------|---|----------------------|-----------------|-------------------|------------|-------------------------|-----------------|-------------------|------------|
| | | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value |
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

Table 12 Outcome at 6 and 12 months in patients who experienced a TIMI hemorrhage at 30 days (N=349)

| Type of Event | Total Enoxa UFH N= 211 N= 138 | Six months follow up | | | | Twelve months follow up | | | |
|---------------|---|----------------------|-----------------|-------------------|------------|-------------------------|-----------------|-------------------|------------|
| | | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value |
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

Table 13 Outcome at 6 and 12 months in patients who had an intracranial hemorrhage at 30 days (N=150)

| Type of Event | Total Enoxa UFH N= 84 N= 66 | Six months follow up | | | | Twelve months follow up | | | |
|---------------|---|----------------------|-----------------|-------------------|------------|-------------------------|-----------------|-------------------|------------|
| | | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value | Enoxaparin n (%) | UFH n (%) | HR (95% CI) | P value |
| Death | | | | | | | | | |
| Recurrent MI | | | | | | | | | |
| CV events | | | | | | | | | |
| Stroke | | | | | | | | | |

N = total number of follow up events; n = number of patients with a follow up event in each treatment group

- Among patients who did NOT experience a primary efficacy endpoint event, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six months (and one year) post randomization (you may use the sample tables below or choose any other way to present the data).

Table 14 One-year deaths among patients who did NOT experience a primary efficacy endpoint event

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 15 One-year recurrent MI among patients who did NOT experience a primary efficacy endpoint event

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Among patients who did experienced a TIMI major hemorrhage event at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six-month (or one-year) post randomization. This data may be quite similar to that in Table 12 (you may use the sample tables below or choose any other way to present the data).

Table 16 One-year deaths among patients who experienced a TIMI major hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event; N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 17 One-year recurrent MI among patients who experienced a TIMI major hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Among patients who did experienced a TIMI minor hemorrhage event at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six months (or one year) post randomization (you may use the sample tables below or choose any other way to present the data).

Table 18 One-year deaths among patients who experienced a TIMI minor hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 19 One-year recurrent MI among patients who experienced a TIMI minor hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Among patients who did experienced an intracranial hemorrhage event at 30 days, please provide data (and analyses) by treatment group regarding the number (proportion) of who patients died or had an MI during the six-month (or one-year) post randomization. This data may be quite similar to that in Table 13 (you may use the sample tables below or choose any other way to present the data).

Table 20 One-year deaths among patients who experienced an intracranial hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|---------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _d (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
 N_d = number (%) of patients who died; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

Table 21 One-year recurrent MI among patients who experienced an intracranial hemorrhage event at 30 days

| Treatment Group | Tot N | Deaths | | | |
|---------------------------|-------|-----------------------|----------------|------------|------------|
| | | N _m (%) | HR 95% C.I. | P value | RRR (%) |
| Enoxaparin | | | | | |
| Unfractionated heparin | | | | | |

Tot N = Total number of patients who did not experience a primary efficacy endpoint event;
 N_m = number (%) of patients who had MI; HR = hazard ratio; C.I. = confidence interval; RRR = relative risk reduction

- Please provide the identification numbers of patients who died, had a non-fatal reinfarction, or a revascularization procedure at clinical trial sites where ≥ 20 patients experienced a primary efficacy endpoint event. Twelve such sites have been identified from the list provided. Please also provide CRFs for these patients if not already submitted.

Clinical Pharmacology

- The sensitivity of the anti-Xa activity based enoxaparin assay is insufficient for determining apparent $t_{1/2\lambda z}$.
- The sensitivity of the anti-IIa activity based enoxaparin assay is insufficient for determining the time profile during the 12-hour dose interval and as a result the ratio of the anti-Xa activity to the anti-IIa activity during a dose interval is unknown for enoxaparin.
- The therapeutic range of enoxaparin plasma concentrations has been defined considering only the anti-Xa activity. A rationale has not been provided in this submission.
- The relative contributions of the anti-IIa- and anti-Xa-activities to the effect of enoxaparin on aPTT have not been defined in this submission.
- The cross-reactivity of F IIa and F Xa for S2239, and CBS3139, respectively, has not been submitted in this submission.
- The contribution of endogenous mucopolysaccharides to background activity appear not to have been determined in plasma.
- With the anti-Xa activity based assay instability was observed when the samples were exposed to room temperature for ≥ 3 hours. A safe time for exposure of the samples to room temperature was not determined. What was the sample handling in studies RP54563Q-142 and RP54563Q-266?
- A single freeze-thaw cycle affects the precision and accuracy of the anti-Xa activity based assay at the 0.25 IU anti-Xa/mL level (study DMPK/FR/2032). Despite that the plasma concentrations were measured to the lowest level of 0.25 IU anti-Xa /mL in study RP54563Q-142.
- The anti-Xa-activity based assay in urine does not meet the precision and accuracy limits and no stability data are available (study IBP/Biodyn 1772RP54563 Enoxaparin). What was the sample handling in Study

RP54563Q-142? Renal clearance and amounts excreted in urine based on the anti-Xa activity have been reported for enoxaparin in study RP54563Q-142. Information on the impact of endogenous mucopolysaccharides to background activity is also not provided.

- The anti-IIa activity of enoxaprin in urine is impacted by freeze/thaw cycling. What was the sample handling in study RP54563Q-142?

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

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796-1130

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

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/s/

Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-138

Sanofi-Aventis U.S. Inc.
Attention: Eddie Li, Ph.D.
Director, Regulatory Affairs
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

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

Name of Drug Product: Lovenox (enoxaparin sodium) Injection

Review Priority Classification: Priority (P)

Date of Application: November 17, 2006

Date of Receipt: November 17, 2006

Our Reference Number: NDA 22-138

This application proposes a new indication of acute ST-Segment Elevation Myocardial Infarction (STEMI) in the labeling.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 17, 2007.

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
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Meg Pease-Fye, MS
Regulatory Health Project Manager
(301) 796-1130

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

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/s/

Edward Fromm

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**sanofi aventis**

Because health matters

6 July, 2006

George Q. Mills, M.D., Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

**IND 31,532; Lovenox® (enoxaparin sodium, injection; RP 54563)
Serial No. 0865**

Re: Action item from the pre-sNDA meeting/communication for the coming sNDA submission for Lovenox in the treatment of acute MI (STEMI) – the availability of the follow-up safety information at the time of sNDA submission

Dear Dr. Mills:

Reference is made to the April 24, 2006 FDA fax and the May 8, 2006 FDA letter in response to our questions posed in the pre-sNDA meeting background package submitted on March 28, 2006 (Serial No. 0855). Sanofi-aventis is providing information referenced in the Question #3 of the submission and in the Action Items of the FDA letter regarding the sponsor's plan to provide the follow-up safety information for the EXTRACT study. Specifically, sanofi-aventis is providing clarification on the extent of follow-up information from the EXTRACT study that will be available to the sponsor at the time of the sNDA submission.

As described in our pre-NDA background package all patients from the EXTRACT trial are to be followed (off drug) until one year post-randomization. Data collection is limited to outcome events of the study. This portion of the trial remains ongoing, with the last patient scheduled to complete follow-up in October 2006. At the time of submission we estimate that 99% of 6-month visit data and 85% of 12-month visit data will have been received by sanofi-aventis and entered into the clinical database. Cleaning and processing of this data is ongoing, and we expect to be able to provide final data on all patients at the time of the 120-day safety update.

Based on the information provided above, does the Agency agree with the sponsor's plan as originally proposed in the March 28, 2006 submission to provide the follow-up information for the EXTRACT study?

Attached is a Form FDA 1571 for this submission.

Sanofi-aventis U.S. Inc. understands that this IND and all information contained therein, unless otherwise made public by Sanofi-aventis U.S. Inc. is confidential.

If you have any questions or comments, please do not hesitate to contact me by telephone (610-889-6554) or by email (eddie.li@sanofi-aventis.com), or in my absence, Jon Villaume, Ph.D. at 610-889-6028.

Sincerely,



Eddie Li, Ph.D.
Regulatory Development Project Leader
Director of Regulatory Affairs
Sanofi-aventis U.S. Inc.
11 Great Valley Parkway
Malvern, PA 19355

cc: Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products

Desk copies: Ms. Diane Leaman, Regulatory Project Manager, Division of Medical Imaging and Hematology Products

Ms. Meg Pease-Fye, Regulatory Project Manager, Division of Cardiovascular and Renal Products



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 31,532

RECEIVED MAY 12 2006

Sanofi-Aventis
Attention: Eddie Li, Ph.D.
Regulatory Development Project Leader
Director of Regulatory Affairs
Sanofi-aventis, U.S., Inc.
11 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Li:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lovenox[®] (enoxaparin sodium) injection.

We also refer to your meeting request dated February 28, 2006 (received March 1, 2006), in which you requested a pre-supplemental NDA meeting to discuss your study entitled "Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment, Thrombolysis in Myocardial Infarction Treatment - TIMI 25 (ExTRACT): A Randomized, Double-Blind, Double-Dummy, Parallel Group, Multinational, Clinical Study to Evaluate the Efficacy and Safety of Enoxaparin Versus Unfractionated Heparin in Patients with Acute ST-segment Elevation Myocardial Infarction."

We further refer to your meeting background package submitted March 28, 2006 (received March 28, 2006).

We further refer to our telefacsimile dated April 24, 2006, in which we provided you with preliminary responses to your questions posed in the March 28, 2006 submission.

Finally, we refer to the telephone conversation between Dr. Eddie Li, Regulatory Development Project Leader, Sanofi-aventis U.S. Inc. and Mrs. Diane Leaman, Regulatory Project Manager, Division of Medical Imaging and Hematology Products on April 27, 2006, in which Dr. Li acknowledged receipt of our responses to the questions posed in the March 28, 2006 submission and requested the meeting scheduled for May 2, 2006, be cancelled. We acknowledge your decision to accept those written responses in lieu of a meeting.

The official responses to that meeting request are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

IND 31,532

Page 2

If you have any questions, call me at (301) 796-1424.

Sincerely,

(See appended electronic signature page)

Diane Leaman, Regulatory Project Manager,
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Questions:

1. *Does the Division agree that the sponsor's proposal for provision of the ExTRACT data set is acceptable?*

FDA Response:

Yes, we agree with your proposal for submitting EXTRACT study reports, analyses and data sets. However, you should also submit full study report, all analyses and data sets for all Phase 2 studies (ASSENT 3, ASSENT 3 Plus, AMI-SK, HART-2, ENTIRE-TIMI-23 and TETAMD).

The regulatory review status (priority or other) will be determined upon preliminary review of the submission.

2. *Does the Division agree with the following content and format of the dossier?*

FDA Response:

Yes

3. *Does the Division agree with the sponsor's plan to provide follow-up safety information for the ExTRACT study?*

FDA Response:

Tentatively, Yes. Please clarify the extent of follow-up information that will be available at the time of your sNDA submission.

4. *Does the Division agree with the sponsor's criteria for determining which events are to be subject of a specific patient narrative to be provided?*

FDA Response:

No. You should provide narratives for the following: patients experiencing any serious and unexpected adverse events; patients experiencing study agent discontinuations due to adverse events; patients discontinuing study participation due to adverse events.

5. *Does the Division agree that case report forms (CRFs) will be provided for only the events for which patient narratives are to be generated?*

FDA Response:

No. Please provide CRFs for the following: all deaths; all patients who had study agent discontinuation due to adverse events; and all patients who discontinued study participation due to adverse events. CRFs must contain all the data available on serious adverse events (e.g., Medwatch forms). Additional CRFs may be requested during review and must be supplied within 7 days.

6. *Does the Division agree with the sponsor's proposal to submit, along with the full ExTRACT study database in electronic format, the following by-subject line listings?*

FDA Response:

Yes. In addition, please include: subjects who discontinued due to serious (possible/probable, etc.) adverse events regardless of causality. Also include subjects who had adjudicated major bleeds.

7. Does the Division agree with the following preparation/presentation of the ExTRACT database?

FDA Response:

- **Tentatively, Yes. The presentation appears to be acceptable as long as the items listed below are sufficiently addressed. Additionally, please confirm that the SAS data sets will contain all the raw data from the CRFs.**
- **The raw data used for pharmacokinetics (PK) and population pharmacokinetics (POP PK) analysis should be included in the submission.**
- **Please submit Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) version 3.1.1 standard datasets.**
- **Please do not split large datasets into 100 megabyte pieces.**
- **All data tables should include sortable patient identifiers.**

DECISIONS (AGREEMENTS) REACHED:

In the April 27, 2006 telephone conversation between Eddie Li and Diane Leaman, in response to the Agency April 24, 2006 telefacsimile, Sanofi-Aventis made the following agreement:

Sanofi-Aventis will provide the required information referenced in Question 7.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

In the April 27, 2006 telephone conversation between Eddie Li and Diane Leaman, in response to the Agency April 24, 2006 telefacsimile, Sanofi-Aventis made the following agreement:

In regard to Question 3, Sanofi-Aventis will clarify the extent of the information that will be available at the time of submission at a later date.

ACTION ITEMS:

Sanofi-Aventis will provide a response to the Agency's request for clarification of further follow-up safety information for the ExTRACT study.

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/s/

Diane V Leaman
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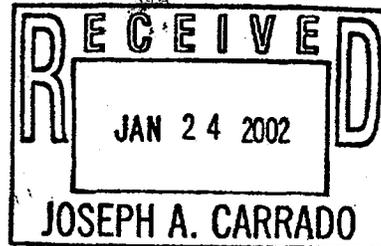
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164

Aventis Pharmaceuticals Inc.
Attention: Joseph A. Carrado, MSc., R.Ph.
Global Drug Regulatory Affairs,
Global Therapeutic Area Head
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800



Dear Mr. Carrado:

Please refer to the meeting between representatives of your firm and FDA on December 14, 2001. The purpose of the meeting was to discuss the proposed Phase 3 ExTRACT study design for the use of Lovenox Injection for the treatment of patients with acute myocardial infarction to reduce death and reinfarction.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

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/s/

Karen Oliver
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MEMORANDUM OF MEETING MINUTES

Meeting Date: December 14, 2001
Time: 1:00 p.m.-3:30 p.m.
Location: Potomac Conference Room, Parklawn Building

Application: NDA 20-164
Lovenox[®] (enoxaparin sodium) Injection

Type of Meeting: Supplement: Discussion of new indication

Meeting Chair: Dr. Kathy Robie-Suh

Meeting Recorder: Ms. Karen Oliver

FDA Attendees, titles, and Office/Division:Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., M.Sc., Acting Division Director
Joyce Korvick, M.D., Deputy Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Ruyi He, M.D., Medical Officer
Min Lu, M.D., Medical Officer
Edvardas Kaminskas, M.D., Medical Officer
Karen Oliver, Regulatory Health Project Manager

Division of Biometrics II (HFD-715)

Thomas Permutt, Ph.D., Statistical Team Leader

External Constituent Attendees and titles:Aventis Pharmaceuticals Products Inc.

Peter Bacher, M.D. Ph.D., CV Clinical Development
Steve Caffé, M.D., US Regulatory Affairs
Joseph Carrado, M.Sc., R.Ph., Global Regulatory Affairs
Eric Chi, Ph.D., Global Regulatory Affairs
Paul Chew, M.D., CV Clinical Development
Santosh Vetticaden, Ph.D., M.D., Global Project Leader
Daisy Chhatwal, Pharm. D., US Regulatory Affairs
Divakar Sharma, Ph.D., Global Statistics

Background:

On October 5, 2001, Aventis Pharmaceuticals Products Inc. requested an End-of-Phase II meeting to discuss the content and format of an upcoming supplemental application to NDA 20-164, Lovenox[®] (enoxaparin sodium) Injection. The meeting was requested to discuss the proposed Phase 3 clinical development plan for the use of Lovenox Injection for the treatment of patients with acute myocardial infarction to reduce death and reinfarction.

The sponsor submitted a two volume background package on November 20, 2001.

Meeting Objectives:

1. To discuss the proposed Phase 3 ExTRACT study design for the use of Lovenox Injection for the treatment of patients with acute myocardial infarction to reduce death and reinfarction.
2. To discuss fast track designation for the proposed supplemental application.

Presentation by the Sponsor: See overhead submitted by the sponsor on 01/17/02

Discussion Points:

In response to the firm's questions in their October 5, 2001 submission, the following agreements were reached after discussion. The format provides the firm's questions, followed by the Agency's responses in bolded lettering.

- Does the Agency concur that the proposed ExTRACT Study design, including objectives, inclusion/exclusion criteria, primary and secondary efficacy outcomes, statistical assumptions and methods, and sample size calculations is acceptable as the single adequate and well-controlled pivotal trial for the intended indication?

No, it does not appear that the trial as currently designed would be adequate.

- **Regarding the study design:**

1. **Comparison of treatment with heparin for 48 hours vs treatment with enoxaparin sodium for 2-8 days, or until discharge, but not greater than 8 days may not be clinically interpretable if clear superiority of enoxaparin sodium with regard to both efficacy and safety in the study is not**

established. Further, consider the following: (a) treatment duration differs significantly between the two treatment arms [48 hours (heparin) vs 2-8 days (Lovenox)]; (b) heparin is not labeled for the specific indication; and (c) safety and efficacy are both extremely important parameters and each must be weighed in the evaluation of whether superiority is shown in the study.

2. The primary efficacy endpoint should be assessed at 30 days. Assessments at 14 days and other timepoints may be secondary analyses. Time-to-event analyses may be of interest as secondary analyses.
 3. Interpretation of the efficacy and safety results may be complicated by having enoxaparin sodium treatment duration range over several days rather than be a specific length of time. It likely will be difficult or impossible to discern the investigator's reason for discontinuing enoxaparin sodium treatment at a particular time. Since this is proposed as an open-label study the likelihood of bias being introduced at this step is high (refer to response to question 3 regarding an open-label study design).
 4. Consider requiring co-administration of aspirin (at a dose of 81-325mg daily), since this is generally a part of the standard of care for acute MI and since there is some evidence that aspirin may give an additional benefit in acute MI when used in combination with thrombolytics. Alternatively, the study could be stratified and sized to clearly demonstrate safety and efficacy with and without aspirin. Note that actual mg dose of aspirin may influence bleeding rate in this study.
 5. Consider conducting this protocol as a double-blind, double-dummy study to minimize bias (see response to question 3).
 6. The definition for major hemorrhage is acceptable. The definition must include a statement that intraocular, retroperitoneal, and intracranial hemorrhages are always considered major hemorrhage.
- In the protocol, clearly describe the 48 hour intervention restriction (see p. 29 of protocol).

- **Provide historical data regarding the percent of AMI patients who undergo diagnostic or therapeutic procedures in the first 48 hours of medical care. The historical data should include country specific information.**
- **Provide information regarding how the proposed dosing regimen for enoxaparin sodium was established.**
- **Define specific times for the monitoring of the following parameters: platelets, hemoglobin, hematocrit.**
- **Clarify whether the formulations and dose regimens of the thrombolytic agents will be those approved in the United States. The labeling would only address use of enoxaparin sodium an adjunct to U.S. approved thrombolytics and regimens.**
- **A total of 16,000 patients being enrolled from 1000 centers will provide an average of 16 patients per center. In the protocol, describe how treatment-by-center interaction will be evaluated.**
- **It appears that any center effect on results may be confounded with specific thrombolytic effect if a particular thrombolytic agent is preferred by a particular center. Explain how this will be addressed.**
- **The protocol specifies that the maximum number of patients per thrombolytic agent will be 6,000. Explain how this is to be accomplished.**
- **Prior heparin use for the acute MI which led to study entry must be addressed as a possible confounder in the analysis of the study results.**
- **Regarding the statistical analysis, clearly describe/define in the statistical analysis plan, the following:**
 - (1) **The proposed "adjusted chi-square" analysis.**
 - (2) **The procedure(s) associated with the interim analysis.**
 - (3) **The procedure(s) for dealing with multiple comparisons.**

- **Provide drug-drug interaction studies between enoxaparin sodium and the thrombolytic agents to be used in the study.**
- **Does the Agency concur that the proposed ExTRACT Study together with all the other supportive studies are sufficient to establish the substantial evidence of efficacy and safety needed to gain marketing approval for the proposed indication?**
- **The acceptance of the single study as a sufficient scientific and regulatory basis for approval of enoxaparin sodium for the desired indication will be determined by its adequacy to support the efficacy claim based on strength of the results (see *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*, May 1998). In general, results from any trial should be independently substantiated.**
- **The size of the proposed study, the multi-center design, and the mortality endpoint are consistent with the single study criteria. However, statistically persuasive data would need to be provided. Results barely significant at usual levels would likely not be considered very persuasive (p 0.05). Accordingly, a larger study might be considered, with sample size calculated on the basis of a smaller level of significance.**
- **Some additional evidence of efficacy appears to be available from other studies. However, the consistency of endpoints between the studies and the single proposed study would be evaluated in the review process. The review process would also give careful attention to the treatment of missing data and patient follow-up.**
- **The applicability of the diverse patient population, standard(s) of care in the countries in this multinational study, and factors influencing the disease process would be evaluated in the review process.**
- **The sponsor proposes the ExTRACT Study to be an open label study since both the efficacy and safety endpoints will be adjudicated by a blinded endpoint committee. Does the Agency concur with this proposal?**
- **Some of the potential biases in an open-label study include:**
 - (1) **Influence on the nature and timing of intervention(s).**
 - (2) **Influence on the objectivity of the investigator.**

- **Consider double-blind, double-dummy design.**
- **Within the protocol, clearly identify the activities and responsibilities of the Data Safety Monitoring Board including membership, how frequently the board meets, how the board communicates to the investigators, ways the safety will be monitored, how frequently the safety will be monitored, and how interactions with the Steering Committee and Critical Event Committee will be regulated.**
- **Within the protocol, clearly identify the activities of the blinded efficacy adjudication board.**
- **Verify that there are two different boards (with different members)-one for safety evaluation the other for efficacy adjudication.**
- Does the Agency concur that the data provided by the sponsor is sufficient justification for Fast Track designation of this supplemental application?
 - **The fast track designation would be determined at filing (Refer to *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*).**
 - **Clarify what would be the advantages of fast track designation at this point in the development of enoxaparin sodium for this indication.**
 - **The type of review (standard vs priority) is determined at the filing meeting [refer to Manual of Policies and Procedures (MAPP) 6020.3 *Priority Review Policy*].**

In response to the sponsor's question regarding labeling, the precise wording of the new clinical indication would be determined during the review process based on the clinical data.