

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-492/S-002**

**Administrative/Correspondence Reviews**

ORIGINAL

July 11, 2003

RECEIVED

JUL 16 2003

DDR-150/CDER

Central Document Room  
 Center for Drug Evaluation and Research  
 Food and Drug Administration  
 Park Bldg., Room 2-14  
 12420 Parklawn Drive  
 Rockville, MD 20857

RECEIVED  
 JUL 15 2003  
 CDR/CDER

Re: *Patent Information for ELOXATIN™ (oxaliplatin)*  
*sNDA 21-492 for the use of oxaliplatin in combination with*  
*infusional 5-FU/LV for the first line therapy of patients with*  
*metastatic carcinoma of the colon or rectum*

Gentlemen:

Pursuant to the provisions of 21 C.F.R. §314.53, applicants of the supplemental new drug application (sNDA) for the use of oxaliplatin in combination with infusional 5-FU/LV for the first line therapy of patients with metastatic carcinoma of the colon or rectum hereby submit information on each patent that claims the drug, drug product, or a method of using the drug product and with respect to which a claim of 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 described in this sNDA.

U.S Patent No.	Expiration Date	Type of Patent	Patent Owner
5,420,319	April 7, 2013	Drug	Debiopharm S.A.
5,338,874	April 7, 2013	Drug	Debiopharm S.A.
5,290,961	January 12, 2013	Drug	Debiopharm S.A.

The following party is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(b) of the Federal Food, Drug and Cosmetics Act and §§314.52 and 314.95 of 21 C.F.R.:

Sanofi-Synthelabo Inc.  
 Patent Counsel  
 9 Great Valley Parkway  
 Malvern, PA 19355

Pursuant to 21 CFR §314.53(d)(2)(ii), the undersigned certifies that U.S. Patent Nos. 5,420,319, 5,338,874 and 5,290,961 information for which was previously submitted in NDA No. 21-492, claim the drug which is the subject of this sNDA.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Paul E. Dupont". The signature is written in a cursive style with a large initial "P".

Paul E. Dupont  
Director, Patents

PED/jmh

Encl: Duplicate copy of letter

### ITEM 13. PATENT INFORMATION

Pursuant to 21 CFR 314.53(d)(4) the patent information for this supplement is being submitted concurrently herewith by separate letter addressed to the Central Document Room.

### REQUEST FOR EXCLUSIVITY

Pursuant to 21 U.S.C. 355(c)(3)(D)(iv) and (j)(4)(D)(iv), and under the provisions of 21 CFR 314.108(b)(5), applicant hereby claims a period of exclusivity of three years from the date of approval of this supplemental application (sNDA) for the use of oxaliplatin in combination with infusional 5-FU/LV for the first line therapy of patients with metastatic carcinoma of the colon or rectum.

In support of this sNDA, applicant has sponsored a clinical investigation (N9741/EFC7462) under investigational new drug application IND 57,004 and certifies that, to the best of its knowledge, said clinical investigation is a new clinical investigation, the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

Applicant further certifies that a thorough search of the scientific literature has been conducted for all published studies or publicly available reports of clinical investigations relevant to the use of oxaliplatin in combination with infusional 5-FU/LV for the first line therapy of patients with metastatic carcinoma of the colon or rectum and that no relevant studies or reports were found. Accordingly, in applicant's opinion and to the best of its knowledge no publicly available information exists to support the approval of the use of oxaliplatin in the indication for which applicant is seeking approval except for the new clinical investigation included in this sNDA. The new clinical investigation is therefore essential to approval of this sNDA.

EXCLUSIVITY SUMMARY for NDA # 21-492 SUPPL # SE1-002

Trade Name ELOXATIN for Injection Generic Name oxaliplatin

Applicant Name Sanofi-Synthelabo, Inc. HFD- 150

Approval Date January 9, 2004

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/\_\_\_/ NO /\_X\_/

b) Is it an effectiveness supplement? YES /\_X\_/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE1

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 /\_X\_/ 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 YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES // NO /\_\_\_/

If yes, NDA #21-492 Drug Name ELOXATIN (oxaliplatin) for Inj.

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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

YES /\_\_\_/ NO /\_\_\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /\_\_\_/ NO /\_\_\_/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /\_\_\_/ NO /\_\_\_/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /\_\_\_/

Investigation #3 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:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

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

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/  
Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/  
Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (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"):

Investigation #\_\_, Study #  
Investigation #\_\_, Study #  
Investigation #\_\_, Study #

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

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

Investigation #1 !  
 !  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
 !  
 !  
 !  
 !

Investigation #2 !  
 !  
 IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
 !  
 !  
 !  
 !

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

Investigation #1 !  
 !  
 YES /\_\_\_/ 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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Christy Cottrell  
Title: Consumer Safety Officer

Date

\_\_\_\_\_  
Richard Pazdur, M.D.  
Division Director

Date

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

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Christy Cottrell  
1/21/04 01:27:02 PM

Richard Pazdur  
1/21/04 03:58:11 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-492 Supplement Type (e.g. SE5): SE1 Supplement Number: 002

Stamp Date: July 11, 2003 Action Date: January 9, 2004

HFD-150 \_\_\_\_\_ Trade and generic names/dosage form: Eloxatin (oxaliplatin) for Injection 50 mg and 100 mg

Applicant: Sanofi-Synthelabo, Inc. Therapeutic Class: P

Indication(s) previously approved: Eloxatin, used in combination with infusional 5-FU/LV is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan. The approval of Eloxatin is based on response rate and an interim analysis showing improved time to radiographic progression. No results are available at this time that demonstrate a clinical benefit, such as improvement of disease-related symptoms or increased survival (see CLINICAL STUDIES).

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

Number of indications for this application(s): 1

Indication #1: In combination with 5-FU/LV for the treatment of patients previously untreated for advanced colorectal cancer

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

Yes: Please proceed to Section A.

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

NOTE: More than one may apply

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

### Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children

- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

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

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
 Christy Cottrell  
 Consumer Safety Officer

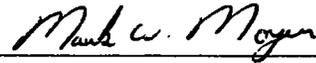
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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Christy Cottrell  
1/15/04 02:14:25 PM

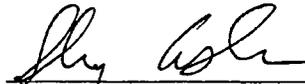
**ITEM 16. DEBARMENT CERTIFICATION**

Sanofi-Synthelabo and National Cancer Institute (NCI) hereby certifies that they did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] of the FD&C Act in connection with this application.



---

Mark Moyer  
Senior Director  
Drug Regulatory Affairs  
Sanofi-Synthelabo



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Sherry Ansher, Ph.D.  
Drug Regulatory Affairs  
National Cancer Institute (NCI)

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-492	Efficacy Supplement Type SE1	Supplement Number 002
Drug: ELOXATIN (oxaliplatin) for Injection		Applicant: Sanofi-Synthelabo, Inc.
RPM: Christy Cottrell		HFD-150 Phone # (301) 594-5761
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		January 11, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Included
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Filing review- 1/6/04
<b>General Information</b>	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H (X) Submitted to DDMAC- under review
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter (X) Burst email
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included- 1-9-04
• Most recent applicant-proposed labeling	Included- 1-9-04
• Original applicant-proposed labeling	Included
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC- 11/20/03 CSO- 1/5/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	12-12-00/8-25-00/6-8-00
• Pre-NDA meeting (indicate date)	5-12-03/5-7-03/1-13-03/3-22-02/ 12-11-01
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A

• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	Included- 1-8-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included- 1-8-04
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Demographic Worksheet (NME approvals only)	Included- 1/6/04
❖ Statistical review(s) (indicate date for each review)	Included- 1-8-04
❖ Biopharmaceutical review(s) (indicate date for each review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Draft included in package- 1/5/04
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	N/A
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	N/A
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested N/A
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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/s/

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Christy Cottrell  
1/16/04 02:48:00 PM

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 21-492                      Supplement # 002                      SE1

Trade Name: ELOXATIN for Injection  
Generic Name: oxaliplatin  
Strengths: 50 mg and 100 mg

Applicant: Sanofi-Synthelabo, Inc.

Date of Application: July 11, 2003  
Date of Receipt: July 11, 2003  
Date clock started after UN: N/A  
Date of Filing Meeting: August 25, 2003  
Filing Date: September 9, 2003  
Action Goal Date (optional): N/A                      User Fee Goal Date: January 11, 2004

Indication(s) requested:                      In combination with 5-FU/LV for the treatment of patients previously untreated for advanced colorectal cancer

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

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification:                      S \_\_\_\_\_                      P   X   \_\_\_\_\_  
Resubmission after withdrawal?                        No                        Resubmission after refuse to file?                        No    
Chemical Classification: (1,2,3 etc.)                        N/A    
Other (orphan, OTC, etc.)                        N/A  

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

Form 3397 (User Fee Cover Sheet) submitted:                      YES  
User Fee ID #                        4553    
Clinical data?                      YES

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?                      YES

If yes, explain: 5-year exclusivity granted for original NDA approval in August 2002

Does another drug have orphan drug exclusivity for the same indication?                      NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?                      N/A

Is the application affected by the Application Integrity Policy (AIP)? NO  
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? N/A

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES  
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES  
If no, explain:

- If an electronic NDA, does it follow the Guidance? YES  
If an electronic NDA, all certifications must be in paper and require a signature.  
Which parts of the application were submitted in electronic format?  
Table of Contents, Labeling, Summary, Clinical, Statistical, Case report tabulations,  
Case report forms, Patent Information, Debarment Certification, User Fee Cover Sheet,  
Financial Information

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A  
If an electronic CTD, all certifications must be in paper and require a signature.  
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? YES,   3   years  
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES  
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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

- Financial Disclosure forms included with authorized signature? YES  
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? YES  
If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 41,817
- End-of-Phase 2 Meeting(s)? Date(s) \_12-12-00/8-25-00/ 6-8-00\_  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) \_5-12-03/5-7-03/1-13-03/3-22-02/12-11-01  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? N/A
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment?  
 If no, did applicant submit a complete environmental assessment?  
 If EA submitted, consulted to Nancy Sager (HFD-357)? NO  
 NO- Not applicable  
 N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

**If 505(b)(2) application, complete the following section:** N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES      NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES      NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES      NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

\_\_\_\_\_ 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.

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

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

\_\_\_\_ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

\_\_\_\_ 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.)

\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

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

YES NO

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

N/A YES NO

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

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

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

YES NO

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

YES NO

• EITHER

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

IND # \_\_\_\_\_ NO

OR

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

N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: August 25, 2003

BACKGROUND:

The original NDA was approved under Subpart H in August 2002 for use in combination with infusional 5-FU/LV as second-line treatment of colorectal cancer. This supplement provides for a new indication in first-line treatment of colorectal cancer.

If approved, this supplement would also convert the accelerated approval to full approval.

ATTENDEES: Amna Ibrahim, Clinical Reviewer  
John Johnson, Clinical Team Leader  
Richard Pazdur, Director  
Grant Williams, Deputy Director  
Ning Li, Acting Statistical Team Leader  
Carolann Currier, DSI  
Joseph Grillo, DDMAC  
Kevin Ridenhour, Clinical Reviewer (observer)  
Christy Cottrell, Consumer Safety Officer

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Amna Ibrahim
Secondary Medical:	John Johnson
Statistical:	Mark Rothmann
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	N/A
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	N/A
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	David Gan
Regulatory Project Management:	Christy Cottrell
Other Consults:	N/A

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

CLINICAL FILE  X  REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES

- Advisory Committee Meeting needed? 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

CLINICAL MICROBIOLOGY N/A FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

STATISTICS FILE  X  REFUSE TO FILE \_\_\_\_\_

BIOPHARMACEUTICS N/A FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

- Biopharm. inspection needed: NO

PHARMACOLOGY N/A FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

- GLP inspection needed: NO

CHEMISTRY N/A FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

- Establishment(s) ready for inspection? N/A
- Microbiology N/A

**ELECTRONIC SUBMISSION:**

Any comments: N/A

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

X  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.

X  Filing issues to be communicated by Day 74.

**ACTION ITEMS:**

➤ Document filing issues/no filing issues conveyed to applicant by Day 74. **DONE- CCOTTRELL**

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

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

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Christy Cottrell  
1/6/04 02:42:41 PM  
CSO

**Cottrell, Christy**

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**From:** Spillman, Dianne D  
**ent:** Monday, January 12, 2004 12:03 PM  
**fo:** 'Mary Wilson'  
**Cc:** Pazdur, Richard; Williams, Grant A  
**Subject:** FDA approves Eloxatin for the initial treatment of advanced colorectal cancer

Mary,

Friday, 1-9-04, the Division approved Eloxatin for use in combination with Infusional 5-FU/LV for the initial treatment of advanced colorectal cancer. Below is the e-mail announcement for distribution to ASCO members.

Please include me on your distribution list when sending out the announcement.

Thanks,  
dianne

=====  
Dianne Spillman  
Special Assistant/Regulatory Project Manager  
Division of Oncology Drugs, HFD-150  
Center for Drug Evaluation & Research, FDA  
ph: (301) 594-5746  
fax: (301) 594-0499  
e-mail: spillmand@cdcr.fda.gov

*From the American Society of Clinical Oncology.*

*In collaboration with the Food and Drug Administration (FDA), and as a service to our members, ASCO will provide information about newly approved therapies for cancer patients. This will allow the agency to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:*

**To:** ASCO membership (domestic USA, embargo date 1/9/04)

**From:** Richard Pazdur, M.D.  
Director, Division of Oncology Drug Products,  
Center for Drug Evaluation and Research, FDA

On January 9, 2004 the U.S. Food and Drug Administration approved oxaliplatin for injection (Eloxatin™, Sanofi-Synthelabo Inc.), for use in combination with Infusional 5-FU/LV for the initial treatment of advanced colorectal cancer. Eloxatin previously received accelerated approval on August 9, 2002 for use in combination with Infusional 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first-line therapy with the combination of Bolus 5-FU/LV and irinotecan.

Safety and efficacy were demonstrated in one multi-center, randomized controlled clinical trial sponsored by the National Cancer Institute as an inter-group study led by the North Central Cancer Treatment Group. The study had 7 arms at different times during its conduct, four of which were closed due to either changes in the standard of care, toxicity or simplification. During the study, the control arm was changed to irinotecan plus Bolus 5-FU/LV. The Eloxatin + Infusional FU/LV regimen was compared to an approved control regimen of irinotecan plus Bolus 5-FU/LV in 531 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. Patients may have received adjuvant therapy for resected Stage II or III disease

without recurrence within 12 months. After completion of enrollment, the dose of irinotecan plus 5-FU/LV was decreased due to toxicity.

The Eloxatin + Infusional FU/LV regimen showed superior survival to the irinotecan plus Bolus FU/LV regimen with median survivals of 19.4 and 14.6 months ( $p=0.0001$ ), respectively. Time to tumor progression and tumor response rate were also superior on the Eloxatin + Infusional FU/LV regimen.

Fatigue, neuropathy, nausea, vomiting, diarrhea, stomatitis, neutropenia and thrombocytopenia were the more common adverse events. Febrile neutropenia or requirement for platelet transfusion were not increased as compared to the irinotecan + Bolus 5-FU/LV. Eloxatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Eloxatin plus 5-FU/LV while on anticoagulants. Patients requiring oral anticoagulants may require closer monitoring. Hypersensitivity has been observed (<2% Grade 3/4) in clinical studies and was usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at [www.fda.gov/cder/foi/label/2004/021492s002lbl.pdf](http://www.fda.gov/cder/foi/label/2004/021492s002lbl.pdf)

The approval announcement itself will also be available at [www.fda.gov/cder/cancer/whatsnew.htm](http://www.fda.gov/cder/cancer/whatsnew.htm)

For further information related to oncology drug approvals, regulatory information, and other oncology resources, please refer to the FDA "Oncology Tools" web site at [www.fda.gov/cder/cancer](http://www.fda.gov/cder/cancer).

*"ASCO periodically e-mails its membership messages of professional interest. If you would prefer not to receive these messages, reply to this e-mail with the word REMOVE in the subject field. You will receive one additional e-mail message to confirm your removal from this e-mail list."*

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**Cottrell, Christy**

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**From:** Spillman, Dianne D  
**Sent:** Monday, January 12, 2004 12:04 PM  
**To:** 'lollar@mailto.nih.gov'  
**Cc:** Pazdur, Richard; Williams, Grant A  
**Subject:** FDA approves Eloxatin for the initial treatment of advanced colorectal cancer

Cindy,

Friday, 1-9-04, the Division approved Eloxatin for use in combination with Infusional 5-FU/LV for the initial treatment of advanced colorectal cancer. Below is the e-mail announcement for distribution to NCI.

Thanks,  
dianne

=====  
Dianne Spillman  
Special Assistant/Regulatory Project Manager  
Division of Oncology Drugs, HFD-150  
Center for Drug Evaluation & Research, FDA  
ph: (301) 594-5746  
fax: (301) 594-0499  
e-mail: spillmand@cder.fda.gov

**From:** Richard Pazdur, M.D.  
Director, Division of Oncology Drug Products,  
Center for Drug Evaluation and Research, FDA

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study patients), which may be fatal. There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Eloxatin plus 5-FU/LV while on anticoagulants. Patients requiring oral anticoagulants may require closer monitoring. Hypersensitivity has been observed (<2% Grade 3/4) in clinical studies and was usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at

[www.fda.gov/cder/foi/label/2004/021492s0021bl.pdf](http://www.fda.gov/cder/foi/label/2004/021492s0021bl.pdf)

The approval announcement itself will also be available at [www.fda.gov/cder/cancer/whatsnew.htm](http://www.fda.gov/cder/cancer/whatsnew.htm)

For further information related to oncology drug approvals, regulatory information, and other oncology resources, please refer to the FDA "Oncology Tools" web site at [www.fda.gov/cder/cancer](http://www.fda.gov/cder/cancer).

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## Cottrell, Christy

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**From:** Spillman, Dianne D  
**Sent:** Monday, January 12, 2004 12:04 PM  
**To:** 'jgalatis@ons.org'; 'jenk@ons.org'  
**Cc:** Pazdur, Richard; Williams, Grant A  
**Subject:** FDA approves Eloxatin for the initial treatment of advanced colorectal cancer

Jon/Jen,

Friday, 1-9-04, the Division approved Eloxatin for use in combination with Infusional 5-FU/LV for the initial treatment of advanced colorectal cancer. Below is the e-mail announcement for distribution to ONS members.

Please include me on your distribution list when sending out the announcement.

Thanks,  
dianne

=====  
Dianne Spillman  
Special Assistant/Regulatory Project Manager  
Division of Oncology Drugs, HFD-150  
Center for Drug Evaluation & Research, FDA  
ph: (301) 594-5746  
fax: (301) 594-0499  
e-mail: spillmand@cder.fda.gov

*In collaboration with the Food and Drug Administration (FDA), and as a service to our members, the Oncology Nursing Society will provide information about newly approved therapies for cancer patients. This will allow the FDA to inform ONS members of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:*

**To:** ONS membership

**From:** Richard Pazdur, M.D.  
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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

(1/5/04)

**DIVISION OF ONCOLOGY DRUG PRODUCTS  
CSO LABELING REVIEW**

**NDA:** NDA 21-492/SE1-002  
**DRUG:** Eloxatin (oxaliplatin) for Injection  
**SPONSOR:** Sanofi-Synthelabo, Inc.  
**DATE OF SUBMISSION:** July 11, 2003, received July 11, 2003

**BACKGROUND:**

This is an SE1 supplement providing for an indication in first-line colorectal cancer.

I compared the proposed labeling to the final printed labeling for the original NDA that was Acknowledged and Retained on October 2, 2002.

**DISCUSSION:**

Only those changes that the sponsor has proposed as part of this supplement were made. There were no additional revisions made to the labeling.

**RECOMMENDATIONS:**

All proposed changes should be reviewed by the appropriate discipline.

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

concurrency:     /dp/ 12-30-03       
Dotti Pease  
Chief, Project Management Staff

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

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Christy Cottrell  
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CSO

Dotti Pease  
1/6/04 07:09:47 AM  
CSO

5 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(4) Draft Labeling

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>
---	--

TO: (Division/Office) HFD-42/DDMAC <b>ATTN: Joe Grillo</b>	FROM: HFD-150/Division of Oncology Christy Cottrell, CSO
---	---

DATE July 25, 2003	IND NO.	NDA NO. NDA 21-492	TYPE OF DOCUMENT SE1-002	DATE OF DOCUMENT July 11, 2003
NAME OF DRUG Eloxatin (oxaliplatin) for Injection		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE December 15, 2003

NAME OF FIRM  
Sanofi-Synthelabo, Inc.

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> LABELING REVISIONS/CLINICAL PHARMACOLOGY & PRECAUTIONS<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG EXPERIENCE

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

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL
  PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

The Division requests that DDMAC review the proposed product labeling and any relevant advertising for this supplemental NDA and attend any necessary meetings. All pertinent documents can be found in the Electronic Document Room under NDA 21-492/SE1-002.

Medical Officer is Amna Ibrahim, M.D.  
 Project Manager is Christy Cottrell.

Package sent electronically by DFS on 7-25-03.

SIGNATURE OF REQUESTER Christy Cottrell	METHOD OF DELIVERY ( <i>Check One</i> ) <input checked="" type="checkbox"/> E-MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

-----  
Christy Cottrell

7/25/03 09:42:52 AM

DDR: Please process this outgoing consult to DDMAC (HFD-42).

All documents are available in the EDR.

**ITEM 2.4**

**Carton Label**

**As requested by FDA in the approval letter dated 9 August 2002 for NDA 21-492, Sanofi-Synthelabo submitted modified carton and container (vial) labels emphasizing the "oxali" prefix in sNDA 21-492/s001 on 2 October 2002. The FDA approved these on 14 January 2003.**

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**ITEM 2.5**

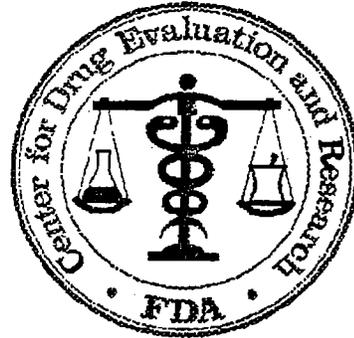
**Vial Label**

As requested by FDA in the approval letter dated 9 August 2002 for NDA 21-492, Sanofi-Synthelabo submitted modified carton and container (vial) labels emphasizing the "oxali" prefix in sNDA 21-492/s001 on 2 October 2002. The FDA approved these on 14 January 2003.

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# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 5

**Date:** 12-17-03

---

**Re:** NDA 21-492/S-002 for Eloxatin- Final minutes of teleconference

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Mark,

Attached are the Division's finalized minutes from our November 3, 2003, teleconference to discuss review issues for Eloxatin, NDA 21-492/S-002.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell



A teleconference with the sponsor was held on September 2, 2003, to discuss the above comment. See minutes of this teleconference for details.

This teleconference was requested in preparation for submission of the requested data tables for new lesions.

#### **DISCUSSION:**

The Division began the discussion by stating that new lesions are integral to establishing a patient as a progressor, and noted that new lesions were not captured anywhere.

The sponsor explained that there were two major categories: 1) patients who progressed while on treatment and developed new lesions while on treatment (~ 100 patients); and 2) patients who went off study for other reasons and progressed later. The sponsor noted that these patients had nothing recorded in the CRFs, but that radiology reports note an increase in liver lesions. The sponsor further explained that there were 301 patients with new lesions that had comments noted in the CRF (96 in the "Comments" section, 217 in the other two panels, and 12 that overlapped). There were 673 progressors, so approximately 40-50% of patients who progressed had new lesions.

The Division inquired whether the sponsor looked specifically at new lesions, and the sponsor replied that they only looked for the reason for progression. The sponsor offered to send radiology reports to the Division, but noted that the only radiology reports available were the ones that were used to define progression. The Division stated that the problem with this situation is that there is no way of assuring that we have identified all new lesions because there was no requirement for documenting new lesions. The Division felt that we could never be completely confident that all new lesions had been identified. The sponsor argued that if the investigator was comprehensive in completing the CRF, then all new lesions would have been identified.

The Division stated that we would need to look at radiology reports for all patients. The sponsor asked which data would be most important for the Division's review. The Division responded that the ideal dataset would contain dates, cycle numbers, measurements, which patients had measurable disease, which patients had evaluable disease, progression of target or non-target, progression based on increase in evaluable disease, or progression based on new lesions. Additionally, the Division requested that the sponsor include a column that identifies whether a patient had new lesions using a numerical designation (i.e., 0 for no new lesions and 1 for new lesions). The Division inquired whether the radiology reports captured any new lesions that did not get into the dataset. The sponsor replied that they had encountered that situation and that in 11 instances, the investigator deemed a patient as a progressor on a certain date, but those patients truly did not meet the criteria for progression at that point.

The Division asked when the sponsor could have the radiology reports together and ready to submit. The sponsor stated that the information on the 301 patients with new lesions was ready for submission immediately, but that they would have to get back to the Division with a timeline for submission of the remainder of the information.

There were no unresolved issues or action items. The teleconference concluded at 2:30 pm.

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Clinical Reviewer

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/s/

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Christy Cottrell  
12/16/03 04:37:56 PM

Amna Ibrahim  
12/17/03 09:51:26 AM

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/s/

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Christy Cottrell  
12/17/03 10:57:48 AM

# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 1

**Date:** 11-25-03

---

**Re:** NDA 21-492/S-002 for Eloxatin

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. Included in this fax are requests for additional information from Dr. Rothmann.

1. For study EFC7233, please submit the estimates of Hazard ratios and 95% confidence intervals, or the number of events in each arm for time-to-progression. Such information was requested in a pre-NDA meeting for all time-to-event endpoints for study 7233.
2. For study EFC2962, please submit the data for the updated survival analysis that was presented at ODAC. This was also requested in a pre-NDA meeting.
3. For study EFC2961, please submit the file Cox 2961 or any file that contains the survival data (131 events) for which the most updated survival analysis was performed and published or previously submitted.

Please submit your response to this query as soon as possible. If you have any questions, feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

-----  
Christy Cottrell  
11/25/03 12:03:48 PM  
CSO

# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 1

**Date:** 11-19-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. Included in this fax is a request for additional information from Dr. Rothmann.

- In the analysis of time-to-progression for the N9741 (7462) study, twelve patients (2 on the IFL arm, 2 on the FOLFOX4 arm and 8 on the IROX arm) were regarded as having events at time zero. Please explain why these twelve patients were listed as having progression events at time zero, or direct us to the location of this information in the supplement if it has already been provided.

Please submit your response to this query as soon as possible. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

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Christy Cottrell  
11/19/03 03:56:52 PM  
CSO

# FAX

**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**

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



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 4

**Date:** 11-12-03

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**Re:** NDA 21-492/S-002 for Eloxatin – Telecon minutes

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Mark,

Attached are the Division's finalized minutes from our September 2, 2003, teleconference during which we discussed a filing issue that was identified for NDA 21-492/S-002.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

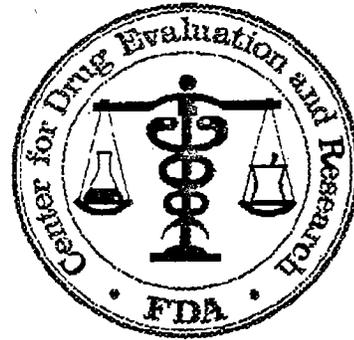
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/s/

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Christy Cottrell  
11/12/03 11:59:03 AM

# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 1

**Date:** 11-4-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. Included in this fax is a request for additional information from Dr. Rothmann.

- Please provide the data that lists the primary site (colon or rectum) for each patient in the N9741 (7462) study. The data should also include the SUBJID variable.

Please submit your response to this query as soon as possible. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

-----  
Christy Cottrell  
11/4/03 11:54:11 AM  
CSO

**From:** Cottrell, Christy  
**Sent:** Friday, October 31, 2003 1:36 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Subject:** Question from Dr. Johnson  
Mark,

Dr. Johnson has the following inquiry:

Many of the non-hematology AEs in the Table CYTOX do not have a grade reported. It appears you did not include these AEs in calculating the incidence numbers in Table 8 in the package insert. If these were not AEs, why are they in the CYTOX Table?

Thanks,  
Christy

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On Original*

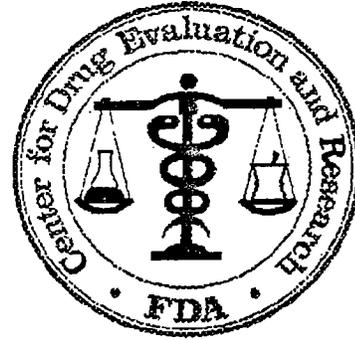
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/s/

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Christy Cottrell  
11/4/03 11:44:38 AM  
CSO

# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 1

**Date:** 10-28-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. Included in this fax is a request for additional information from Dr. Johnson.

1. Are the Adverse Experience tables in the package insert based on all treatment emergent AEs or only AEs possibly related to drug treatment?
2. For AE Tables 8, 9, 12, and 14 in the package insert, please indicate how each table was generated. What is the table containing the primary data? What queries were done on the primary table to generate the numbers in the AE tables in the package insert?

Please submit your response to this query as soon as possible. If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

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Christy Cottrell  
10/28/03 10:09:52 AM  
CSO



**FILING ISSUES IDENTIFIED**

NDA 21-492/S-002

9/17/03

Sanofi-Synthelabo, Inc.  
9 Great Valley Parkway  
P.O. Box 3026  
Malvern, PA 19355

Attention: Mark Moyer  
Senior Director, Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your July 11, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eloxatin (oxaliplatin for injection).

We also refer to your electronic mail submissions dated August 12 and September 4 and 11, 2003.

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 September 9, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The regimen FOLFOX 4 used in your NDA requires a combination of oxaliplatin, leucovorin and bolus and infusional 5-FU. However, a number of patients have incomplete information about leucovorin and 5-FU, as it was not recorded in the CRF. Documentation of administration of these agents is required. We suggest the following:

Information for leucovorin, and if applicable for 5-FU, should be obtained from the clinic or hospital records on a pre-specified 50 responders on each of the IFL and FOLFOX4 arms. Information on all cycles up to a maximum 10 cycles should be collected. Information to be sent to us should include clinical ID number, date, drug name, dose (numeric), and treatment arm. This information should be submitted to us as a SAS transport file.

The first 50 responders (by patient ID numbers) should be selected on the IFL arm. The responding patients' ID numbers in the FOLFOX4 arm for whom the information is required are:

7462 2249 086515	7462 2205 080282
7462 2204 083904	7462 1300 081016
7462 1128 088928	7462 1126 084627
7462 1118 084952	7462 1066 083596
7462 1036 085158	7462 0558 087058
7462 0558 086363	7462 0174 079610
7462 0169 078845	7462 0165 080725
7462 0163 084792	7462 0135 090228
7462 0098 084474	7462 0083 079380
7462 0422 094875	7462 0422 094596
7462 0422 091762	7462 0370 093331
7462 0363 094647	7462 0363 093127
7462 0330 090685	7462 0330 090165
7462 0269 088615	7462 0254 094482
7462 0254 091366	7462 0197 094906
7462 0197 094019	7462 0197 085180
7462 0196 095204	7462 0196 093433
7462 0172 094083	7462 0172 088526
7462 0169 092884	7462 0164 089560
7462 0163 095223	7462 0163 090398
7462 0152 089432	7462 0125 092680
7462 0120 089036	7462 0096 091529
7462 0083 092395	7462 0077 094571
7462 0020 089741	7462 0008 094378
7462 0008 089500	7462 0000 094355

2. There is no information regarding new lesions in the CRFs or the electronic datasets. In order for response rate and time-to-progression (TTP) results to be included in the label, information about new lesions must be submitted. Response rate and TTP analyses are also important for evaluating the cross-over effect on the survival analysis, in which CPT-11 was available to all patients receiving FOLFOX 4, but few patients on the IFL arm were able to obtain oxaliplatin as second-line therapy.

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

We do not expect a response to this letter, and we acknowledge that your submissions dated August 12, September 4, and 11, 2003, addressed the issues outlined above. The submissions will be reviewed with this supplement.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

*{See appended electronic signature page}*

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

-----  
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/s/

-----  
Richard Pazdur  
9/17/03 02:25:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-492/S-002

9/9/03

Sanofi-Synthelabo, Inc.  
9 Great Valley Parkway  
P.O. Box 3026  
Malvern, PA 19355

Attention: Mark Moyer  
Senior Director, Drug Regulatory Affairs

Dear Mr. Moyer:

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

Name of Drug Product:	Eloxatin (oxaliplatin for injection)
NDA Number:	21-492
Supplement number:	002
Review Priority Classification:	Priority (P)
Date of supplement:	July 11, 2003
Date of receipt:	July 11, 2003

This supplemental application proposes the following change: A new indication in patients previously untreated for advanced colorectal cancer.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 9, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 11, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room  
1451 Rockville Pike  
Rockville, Maryland 20854

If you have any question, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

*{See appended electronic signature page}*

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

-----  
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/s/

-----  
Christy Cottrell  
9/9/03 10:42:04 AM  
Signing for Dotti Pease

9-4-03 email from Aibrahim to MMoyer re New Lesions .txt

From: Ibrahim, Amna  
Sent: Thursday, September 04, 2003 12:16 PM  
To: 'mark.moyer@us.sanofi.com'; Cottrell, Christy; Ibrahim, Amna  
Subject: RE: New Lesions ?

Hello Mark

Thank you for your response. Three examples have been given in the word attachment. In the 3rd example it is assumed that brain is a new site for metastasis, because it was not reported at baseline.

- 1-Is there any dataset or any place in the CRF where ALL baseline lesions were recorded, irrespective of whether they were target, non-target, measurable or non-measurable lesions?
- 2-How many patients were recorded as having progression based on assumptions?

Thanks  
Amna

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

From: mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
Sent: Thursday, September 04, 2003 11:14 AM  
To: cottrellc@cdcr.fda.gov; ibrahima@cdcr.fda.gov  
Subject: New Lesions ?

On August 26, 2003, Sanofi-Synthelabo received a fax from the FDA with the following request (bolded):

In order for response rate and time-to-progression (TTP) results to be included in the label, information about new lesions must be submitted. Response rate and TTP analyses are also important for the cross-over issue in the survival analysis, in which CPT-11 was available to all patients receiving FOLFOX4, but few patients on the IFL arm were able to obtain oxaliplatin as second-line therapy.

There is no information regarding new lesions in the CRFs or the electronic datasets. Please submit a proposal addressing the lack of new lesion information prior to September 4, 2003, so we may have time to review it prior to the filing date.

In response to your fax dated August 26, 2003 and as a follow-up to our teleconference on September 2, 2003, Sanofi-Synthelabo has prepared the attached response (as a word document) that details where in the current sNDA database new lesion information can be derived. In addition, attached as a separate pdf file are the corresponding annotated case report forms.

Also, for the purpose of internal review and convenience, Sanofi-Synthelabo has prepared limited patient profiles that show the basis for progression of each patient. In the attached response, we have included three representative patient profiles with progression information for FDA's review and comment. These profiles are derived from the datasets submitted in the sNDA.

During our teleconference, Sanofi-Synthelabo reported results of our review to identify patients whose basis for progression was solely due to new lesions on Arms A + F. Following Dr. Johnson's comments regarding the incidence of new lesions in this population, we have started a review of the data to determine the basis for all progressions. In addition to allowing us to estimate the incidence of new lesions, this review will clarify the reason for progression in each patient. Results will be provided to FDA when the review is completed, and further discussions can then take place if anything additional needs to be addressed.

9-4-03 email from AIBrahim to MMoyer re New Lesions .txt  
Please provide any comments on the representative profiles. If the FDA finds these profiles useful for review, Sanofi-Synthelabo will submit the patient profiles for all patients with progression, or a FDA selected subset of patients with progression. These can be available for submission by early next week, dependant on implementation of any FDA comments/request.

As an update to your request on August 7, 2003, Sanofi-Synthelabo plans to submit the dataset with available information on the patients for which leucovorin dosing and 5-FU bolus and infusion data were requested on Friday, September 5, 2003.

Finally, thank you for sending the list of patients with multiple progression dates. Sanofi-Synthelabo will review this list and respond accordingly.

(See attached file: NEW LESION PROPOSAL\_VERSION3.doc)(See attached file: CRF's.pdf)

Kind Regards,

Mark Moyer  
Sr. Director, Drug Regulatory Affairs- Oncology Sanofi-Synthelabo  
(610) 889 6417

Important: The Information in this e-mail belongs to Sanofi-Synthelabo Inc., is intended for the use of the individual or entity to which it is addressed, and may contain information that is privileged, confidential, or exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or use of, or reliance on, the contents of this e-mail is prohibited. If you have received this e-mail in error, please notify us immediately by replying back to the sending e-mail address, and delete this e-mail message from your computer.

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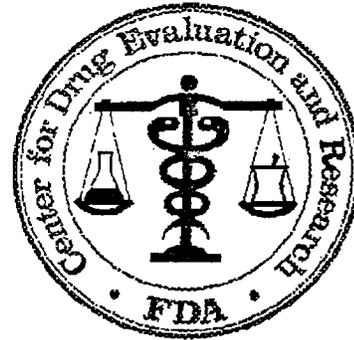
/s/

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Christy Cottrell  
9/4/03 01:50:26 PM  
CSO

# FAX

**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**

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



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 3

**Date:** 9-3-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. In follow-up to our teleconference on September 2, 2003, attached are the ID numbers for the 31 patients that had multiple progression dates.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

CLIN ID	PG DATE
7462 0083 079380	08/22/2000
7462 0083 079380	12/15/1999
7462 0165 080725	12/13/2000
7462 0165 080725	07/27/2000
7462 0485 083428	09/15/2000
7462 0485 083428	02/14/2000
7462 0165 083595	01/16/2001
7462 0165 083595	04/21/2000
7462 1035 083670	09/21/2000
7462 1035 083670	11/23/1999
7462 1021 084910	05/15/2000
7462 1021 084910	11/20/2000
7462 1922 085029	09/12/2000
7462 1922 085029	10/11/2000
7462 0968 086350	05/09/2000
7462 0968 086350	07/17/2000
7462 0996 086702	04/04/2000
7462 0996 086702	03/28/2000
7462 0558 087058	05/01/2001
7462 0558 087058	02/05/2002
7462 0558 087058	06/13/2001
7462 0120 087351	03/26/2001
7462 0120 087351	08/30/2000
7462 0269 088949	09/12/2000
7462 0269 088949	01/22/2001
7462 2300 090164	05/14/2001
7462 2300 090164	03/03/2001
7462 2327 090512	03/28/2001
7462 2327 090512	02/16/2001
7462 1184 090718	02/01/2001
7462 1184 090718	10/27/2000
7462 2341 090810	03/14/2001
7462 2341 090810	10/18/2001
7462 1038 091161	11/24/2000
7462 1038 091161	04/16/2001
7462 2236 091384	09/04/2001
7462 2236 091384	12/05/2000
7462 2365 091605	11/26/2001
7462 2365 091605	09/06/2001
7462 2366 091606	10/03/2001
7462 2366 091606	06/01/2001
7462 2362 092384	12/17/2001
7462 2362 092384	05/06/2002
7462 1184 092390	12/05/2001

CLIN ID	PG DATE
7462 1184 092390	05/07/2001
7462 0558 092536	05/03/2001
7462 0558 092536	02/08/2001
7462 0558 092631	03/26/2002
7462 0558 092631	12/06/2001
7462 0300 092780	10/08/2001
7462 0300 092780	04/10/2001
7462 1387 092942	09/06/2002
7462 1387 092942	09/24/2001
7462 2173 094107	12/19/2001
7462 2173 094107	07/17/2001
7462 0169 094120	02/13/2002
7462 0169 094120	11/01/2001
7462 1278 094269	05/30/2002
7462 1278 094269	01/31/2002
7462 1811 094375	02/06/2002
7462 1811 094375	10/19/2001
7462 2253 094980	10/05/2001
7462 2253 094980	08/10/2001

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/s/

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Christy Cottrell  
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# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

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**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

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**Pages, including cover sheet:** 1

**Date:** 8-26-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. This fax details a filing deficiency that the team identified during our internal filing meeting yesterday.

- In order for response rate and time-to-progression (TTP) results to be included in the label, information about new lesions must be submitted. Response rate and TTP analyses are also important for the cross-over issue in the survival analysis, in which CPT-11 was available to all patients receiving FOLFOX 4, but few patients on the IFL arm were able to obtain oxaliplatin as second-line therapy.

There is no information regarding new lesions in the CRFs or the electronic datasets. Please submit a proposal addressing the lack of new lesion information prior to September 4, 2003, so we may have time to review it prior to the filing date.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

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/s/

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Christy Cottrell  
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CSO  
Fax sent on 8-26-03

# FAX

**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**

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



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**To:** Mark Moyer

**From:** Christy Cottrell

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**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

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**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

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**Pages, including cover sheet:** 1

**Date:** 8-13-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your pending supplemental NDA 21-492/S-002 for Eloxatin. We received your e-mail correspondence of August 12, 2003 that provided information on Sanofi's preparation to respond to the Division's request for additional dosing data.

The patient selection is acceptable. We understand that you may not be able to send us the requested data by the filing date. We would prefer to receive the requested data all together. Before September 9<sup>th</sup>, we ask that you provide us with the date by which you can submit this information.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

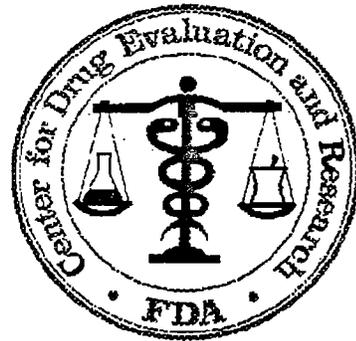
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Christy Cottrell  
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# FAX

**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

**To:** Mark Moyer

**From:** Christy Cottrell

---

**Fax:** (610) 889-6993

**Fax:** (301) 594-0499

---

**Phone:** (610) 889-6417

**Phone:** (301) 594-5761

---

**Pages, including cover sheet:** 2

**Date:** 8-7-03

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**Re:** NDA 21-492/S-002 for Eloxatin

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Mark,

Please refer to your NDA 21-492/S-002 for Eloxatin. Included in this fax is a request for additional information needed *prior to filing* from the clinical reviewer.

If you have any questions, please feel free to call me at (301) 594-5761.

Thanks,

Christy Cottrell

NDA 21-492, serial # 002 was submitted on July 11, 2003. During our initial review, we have found a major deficiency, as discussed with you on July 30<sup>th</sup>, and August 1<sup>st</sup>, 2003. The regimen FOLFOX 4 used in your NDA requires a combination of oxaliplatin, leucovorin and bolus and infusional 5-FU. However, a number of patients have incomplete information about leucovorin and 5-FU, as it was not recorded in the CRF. Documentation of administration of these agents will be required for the filing of your NDA. We suggest the following:

Information for leucovorin, and if applicable for 5-FU should be obtained from the clinic or hospital records on prespecified 50 responders on each of the IFL and FOLFOX arms. Information on all cycles up to a maximum 10 cycles should be collected. Information to be sent to us should include clinical ID, agent, date, dose (numeric) and treatment arm. This information should be submitted to us as a SAS transport file.

The first 50 responders (by patient ID numbers) should be selected on the IFL arm. The responding patient ID numbers in the FOLFOX arm for whom the information is required are:

7462 2249 086515	7462 2205 080282
7462 2204 083904	7462 1300 081016
7462 1128 088928	7462 1126 084627
7462 1118 084952	7462 1066 083596
7462 1036 085158	7462 0558 087058
7462 0558 086363	7462 0174 079610
7462 0169 078845	7462 0165 080725
7462 0163 084792	7462 0135 090228
7462 0098 084474	7462 0083 079380
7462 0422 094875	7462 0422 094596
7462 0422 091762	7462 0370 093331
7462 0363 094647	7462 0363 093127
7462 0330 090685	7462 0330 090165
7462 0269 088615	7462 0254 094482
7462 0254 091366	7462 0197 094906
7462 0197 094019	7462 0197 085180
7462 0196 095204	7462 0196 093433
7462 0172 094083	7462 0172 088526
7462 0169 092884	7462 0164 089560
7462 0163 095223	7462 0163 090398
7462 0152 089432	7462 0125 092680
7462 0120 089036	7462 0096 091529
7462 0083 092395	7462 0077 094571
7462 0020 089741	7462 0008 094378
7462 0008 089500	7462 0000 094355

A priority status is requested for this NDA. The above information will be required as soon as possible. Please apprise of the date by which you can submit this information.

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/s/

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Christy Cottrell  
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CSO

## MEMORANDUM OF TELECON

**DATE:** November 5, 2003

**APPLICATION NUMBER:** NDA 21-492/S-002

**DRUG:** Eloxatin (oxaliplatin) for Injection

**BETWEEN:**

Dr. Richard Pazdur, Director  
Christy Cottrell, Consumer Safety Officer

**AND**

Mark Moyer, Regulatory Affairs  
**Representing:** Sanofi-Synthelabo, Inc.

**SUBJECT:** Discussion of Eloxatin supplement with NCCTG

**DISCUSSION:**

Dr. Pazdur began the discussion by stating that the NCCTG would be coming to the Division to discuss data recording problems and accepting this type of incomplete data from cooperative groups.

Dr. Pazdur stated that the Division would like to use the 1<sup>st</sup> line Eloxatin supplement as an example during discussions with NCCTG and requested concurrence from the sponsor. Dr. Pazdur further explained that the Division would not discuss approvability of the application, interpretation of the trial or the specific contents of the supplement. Mr. Moyer agreed and stated that he felt it would be helpful for the Division to talk with NCCTG directly. Dr. Pazdur closed the discussion by reiterating that the Division will not discuss any confidential information with NCCTG.

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Christy Cottrell  
Consumer Safety Officer

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/s/

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Christy Cottrell  
12/9/03 03:10:47 PM

## MEMORANDUM OF TELECON

**DATE:** September 2, 2003

**APPLICATION NUMBER:** NDA 21-492/S-002

**DRUG:** Eloxatin (oxaliplatin for injection)

**SPONSOR:** Sanofi-Synthelabo, Inc.

**BETWEEN:**

Dr. Richard Pazdur, Director  
Dr. John Johnson, Clinical Team Leader  
Dr. Amna Ibrahim, Clinical Reviewer  
Dr. Mark Rothmann, Statistical Reviewer  
Christy Cottrell, Consumer Safety Officer

**AND**

Dr. Bob Bigelow, Statistician  
Dr. Liji Shen, Statistician  
Dr. Paul Juniewicz, Project Direction  
Dr. Sunil Gupta, Clinical Research  
Brenda Kozan, Regulatory Affairs  
Mark Moyer, Regulatory Affairs

**SUBJECT:** Filing issue identified for NDA 21-492/S-002

**BACKGROUND:**

On August 26, 2003, the Division sent the following comment to the sponsor:

- In order for response rate and time-to-progression (TTP) results to be included in the label, information about new lesions must be submitted. Response rate and TTP analyses are also important for the cross-over issue in the survival analysis, in which CPT-11 was available to all patients receiving FOLFOX 4, but few patients on the IFL arm were able to obtain oxaliplatin as second-line therapy.

There is no information regarding new lesions in the CRFs or the electronic datasets. Please submit a proposal addressing the lack of new lesion information prior to September 4, 2003, so we may have time to review it prior to the filing date.

This teleconference was held in follow-up to this comment.

**DISCUSSION:**

The Division began by noting that approximately 30 patients in the dataset had 2 or more progression dates listed. The Division agreed to send the ID numbers for these patients to the sponsor for clarification of actual progression dates.

The Division asked whether any documentation (i.e., scans) was available for the 20 patients (12 in Arm A and 8 in Arm B) for whom there was no documentation of new lesions. The sponsor replied that the algorithms are complicated, with PR having a different algorithm than CR and SD. The sponsor further noted that some sites may have used the WHO criteria to define progression instead of the NCCTG criteria as outlined in the protocol. The Division explained that if there is no documentation, but there is a progression date identified, we would want some kind of documentation. The Division further noted that the discrepancy seems to be a result of how the progression was calculated. The sponsor agreed and stated that scans are not likely to provide any additional information. The sponsor explained that patient profiles on all progressors may be useful, since for many of the progressors, their new lesions were only noted in the Comments field of the CRFs. The sponsor offered to send patient profiles for all patients with progression to include tumor measurements and any relevant comments from the Comment field of the CRFs. The Division agreed that the patient profiles would be helpful.

---

Christy Cottrell  
Consumer Safety Officer

Concurrence:

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Amna Ibrahim, M.D.  
Medical Officer

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/s/

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Christy Cottrell  
10/29/03 03:34:59 PM

Amna Ibrahim  
10/30/03 08:27:07 AM

## MEETING MINUTES

**MEETING DATE:** December 12, 2000    **TIME:** 8:30 am    **LOCATION:** E

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 11-16-00

**Briefing Document Submission Date:** 12-4-00

**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### TYPE OF MEETING:

1. End-of-Phase 2 meeting #4
2. **Proposed Indication:** First line colorectal cancer

### FDA PARTICIPANTS:

Dr. Richard Pazdur, Division Director  
Dr. John Johnson, Medical Team Leader  
Dr. Amna Ibrahim, Medical Officer  
Dr. Mark Rothmann, Statistics Reviewer  
Dr. Atik Rahman, Biopharmaceutics Reviewer  
Dr. Nancy Sher, Medical Officer  
Christy Wilson, Consumer Safety Officer  
Patricia Delaney, Office of Special Health Issues  
Janelle Ernat, Office of Special Health Issues

### INDUSTRY PARTICIPANTS:

Dr. Martine Baysses, Clinical Research, Debiopharm  
Dr. Sunil Gupta, Clinical Research  
Dr. Richard Gural, Drug Regulatory Affairs  
Dr. Alain Herrera, Oncology Business Unit  
Dr. Nathalie LeBail, Clinical Research, Debiopharm  
Mark Moyer, Drug Regulatory Affairs

### MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated December 4, 2000.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

- 1. Sanofi-Synthelabo plans to suspend accrual to the compassionate use study while accrual is ongoing in the four registration studies. If the compassionate use study is reopened during the evaluation phase of the registration studies, there is a potential impact on the primary endpoint of overall survival in EFC4584 and EFC4585. Therefore, does the Division agree that the compassionate use study should not be reopened until the evaluations are completed for the primary overall survival endpoint in these two studies (EFC4584 and EFC4585)?**

**Does the Division agree that it is in the best interest of the registration studies to suspend accrual to the compassionate use study?**

**FDA RESPONSE:**

- The company should use its discretion to balance accrual against continued access outside the trials. We agree that eligible patients should be enrolled in the ongoing clinical trials.
- 2. Does the FDA have any comments on the proposed third line studies? (See attached protocol concept sheets).**

**FDA RESPONSE:**

- Clinical Benefit Assessment (CBA) based on Time to Symptomatic *Worsening* would not be meaningful in a non-randomized trial. However, CBA based on Symptomatic *Improvement* may be used, since it would not be expected that patients would have improvement in symptoms without response to treatment. The components of, as well as interpretation of symptomatic improvement should be defined.

***Discussion: Sponsor agrees.***

- The effect of oxaliplatin would be better demonstrated by a randomized trial of oxaliplatin + 5-FU/LV vs. 5-FU/LV (Protocol EFC4760). Primary endpoint would be response rate at a specified time period (1<sup>st</sup> or 2<sup>nd</sup> evaluation).
- We suggest performing hematology and serum electrolytes more frequently than every 3 weeks.
- Since an adverse effect of oxaliplatin may be pulmonary fibrosis which can be fatal, consider excluding patients with symptomatic pulmonary fibrosis from these third line studies.

**ADDITIONAL COMMENTS**

- In the two randomized trials, we suggest you include patients with both measurable and non-measurable disease. Response rate should be evaluated only in patients with measurable disease.
- Please provide your Clinical Pharmacology and Biopharmaceutics development plan for the use of oxaliplatin alone and/or in combination for your proposed indications in advanced colorectal cancer.

**ACTION ITEMS**

- Sponsor will provide a proposal for final FDA review and agreement regarding the compassionate use program prior to the meeting with the patient advocacy groups in January 2001.

The meeting concluded at 9:45 am.

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

/s/

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Christy Wilson  
2/7/01 03:42:18 PM

Amna Ibrahim  
2/8/01 02:17:48 PM

## INTERNAL MEETING MINUTES

**MEETING DATE:** August 25, 2000      **TIME:** 9:30 am      **LOCATION:** I

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 07-21-00  
**Briefing Document Submission Date:** 07-21-00  
**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### **TYPE OF MEETING:**

1. End-of-Phase 2 meeting #3
2. **Proposed Indication:** First line colorectal cancer

**FDA PARTICIPANTS:** Dr. John Johnson, Medical Team Leader  
Dr. Amna Ibrahim, Medical Reviewer  
Dr. Richard Pazdur, Division Director  
Dr. Gang Chen, Statistics Team Leader  
Dr. Mark Rothmann, Statistics Reviewer  
Christy Wilson, Consumer Safety Officer

### **MEETING OBJECTIVES:**

Discuss sponsor's questions in briefing document dated July 21, 2000.

### **QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. Does the Division agree with the proposed statistical analysis for the final analysis of survival?

#### **FDA RESPONSE:**

- Yes.

**In addition, Sanofi-Synthelabo would like to know the Division's position on having all analyses performed with a one-sided test?**

#### **FDA RESPONSE:**

- No.

2. Does the Division agree that a comparison of the single agent oxaliplatin arm (Arm B) to the 5-FU/LV alone arm (Arm A), and the comparison of the oxaliplatin alone arm (Arm B) to the 5-FU/LV + oxaliplatin arm (Arm C) does not need to be performed to support the potential submission for conditional approval?

**FDA RESPONSE:**

- Yes.
- Survival is a clinical endpoint and an improvement in survival for this endpoint would suffice for full approval. Conditional approval is not anticipated.

3. Does the Division agree with the use of this minimization technique for treatment allocation?

**FDA RESPONSE:**

- Because a patient's known characteristics may dictate which treatment they will receive, minimization (particularly when Center is used as stratification factor) can lead to bias with respect to non-stratified factors. If a patient's characteristics dictate that they will be in the control group, they may be dissuaded from entering the study (they can always receive this treatment without being on study). As a stratification factor, we prefer country/region instead of center.

4. Does the Division agree that this is acceptable?

**FDA RESPONSE:**

- Yes.

Sanofi-Synthelabo plans to submit the statistical analysis plan prior to any patient entry; does the Division agree that this timing is acceptable?

**FDA RESPONSE:**

- Yes.

5. Does the FDA agree with this change in proposed patient population?

**FDA RESPONSE:**

- Yes.

**6. Does the Division agree that the prior dosing information does not need to be collected in this randomized Phase III study?**

**FDA RESPONSE:**

- Yes. However, the following should be collected: Start and stop dates for prior therapy, whether response was achieved and the date of response, and date of progression of disease.

**7. Does the Division have any additional comments regarding this protocol and the statistical analyses proposed?**

**FDA RESPONSE:**

- We recommend that the final analysis be performed based on a pre-specified total number of deaths between the 5-FU/LV arm and the combination arm.
- Informative censoring (censoring subjects who receive second-line therapy) violates the censoring assumptions needed for the log-rank (Wilcoxon) test and Kaplan-Meier estimation. Such results will not be interpretable – p-values and estimates are calculated based on assumptions that do not hold.
- Cause and effect relationships cannot be drawn from adjusting one response variable (survival) by another response variable (second-line treatment included as a time dependent covariate).
- Subgroup analyses are strongly discouraged. All subgroup analyses should be pre-specified with multiplicity adjustments, not post-hoc – determined by baseline factors associated with higher or lower probabilities of receiving second-line therapy.
- Definition of time to worsening for Clinical Benefit: Death without worsening should be censored and not counted as an event.
- In Table 2, 4/8, worsening must persist for 4 weeks or until death or Disease Progression. However, improvement must persist for 4 weeks *without* death or progressive disease.
- Each component of clinical benefit response should be analyzed separately in addition to the combined components.
- Cross-over design will not be acceptable to review the protocol for survival as an endpoint (discussed at the meeting with NCI).
- In the event of Grade IV diarrhea, dose modification *should* occur with the *next* cycle. (refer to section 5.1.5.1.2, page 28/102 of protocol)

- Because of propensity for diarrhea, electrolyte panel could be included in the routine laboratory blood work. Abnormal electrolytes could possibly affect performance status by causing weakness and lethargy.
- Suggest including the duration of adverse event in section 9.3.3 when evaluating safety.

**8. A) Does the Division agree with this proposal?**

**B) Does the Division have any recommendations regarding how best to address this as an alternative endpoint for full approval in the protocol and/or statistical analysis plan?**

**FDA RESPONSE:**

- There can be only one primary endpoint. Classically, survival benefit has been the primary endpoint for approvability. Clinical benefit response assessment can be a secondary endpoint. Clinical benefit has not been the basis for marketing approval for any drug for this use. However, it may be used to demonstrate approvability if clinical benefit is shown in case the primary endpoint of survival is not met, provided:
  - ◆ It is supported by better RR and TTP.
  - ◆ It is a very large effect or confirmed in a 2<sup>nd</sup> randomized, controlled trial.
- Clinical benefit is subjective and the trial is not blinded. The clinical benefit response assessment endpoints must be pre-specified in the protocol. Symptoms to be used to show this clinical benefit must also be pre-specified. These have been provided by the sponsor in the second meeting package.

**9. A) Does the Division agree that this is adequate to support this endpoint as an alternative endpoint to support full approval?**

**FDA RESPONSE:**

- The detailed analysis methods should be included in the statistical analysis plan, which is submitted prior to the randomization of the first patient to treatment.

**B) Would the Division require pre-specified null and alternative hypotheses for the clinical benefit response rate and time to worsening?**

**FDA RESPONSE:**

- Yes.

**10. Does the Division have any specific comments/concerns regarding the proposed case report forms?**

**FDA RESPONSE:**

- To be given after protocol is resubmitted.

**OTHER COMMENTS**

- ◆ TTF should be removed as a secondary endpoint.
- ◆ Please refer to the NCI discussion where correlations for time to disease related symptom progression were addressed.

There were no action items or unresolved issues. The meeting concluded at 10:30 am.

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

/s/

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Christy Wilson  
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Amna Ibrahim  
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**MEETING MINUTES**

**MEETING DATE:** June 8, 2000

**TIME:** 9:30 am

**LOCATION:** G

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 04-11-00

**Briefing Document Submission Date:** 05-18-00

**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin (SR96669)

**SPONSOR/APPLICANT:** Sanofi Pharmaceuticals, Inc.

**TYPE OF MEETING:**

1. End-of-Phase 2
2. **Proposed Indication:** First line colorectal cancer

**FDA PARTICIPANTS:**

Dr. Richard Pazdur, Division Director, HFD-150 (industry- only)  
Dr. John Johnson, Medical Team Leader, HFD-150  
Dr. Steven Hirschfeld, Medical Reviewer, HFD-150  
Dr. Fumitaka Nagamura, Medical Fellow, HFD-150  
Dr. Gang Chen, Statistics Team Leader, HFD-150 (industry- only)  
Dr. Mark Rothmann, Statistics Reviewer, HFD-150  
Christy Wilson, Consumer Safety Technician, HFD-150  
Dr. Eric Duffy, Chemistry Team Leader, HFD-150  
Dr. James Krook, ODAC (pre- only)

**INDUSTRY PARTICIPANTS:**

Dr. Robert Bigelow, Statistics, Sanofi  
Dr. Richard Gural, Drug Regulatory Affairs, Sanofi  
Dr. Nassir Habboubi, Clinical Research, Sanofi  
Mark Moyer, Drug Regulatory Affairs, Sanofi  
Dr. Nathalie LeBail, Clinical Research, Debiopharm  
Dr. Martine Bayssas, Debiopharm Clinical Research  
Dr. Sunil Gupta, Medical Affairs, Sanofi  
[ ]  
Dr. Alain Herrera, Oncology Business Unit, Sanofi  
Dr. Thomas Strack, Regulatory Affairs, Lilly  
[ ]  
Dr. Percy Ivy, NCI Representative

**MEETING OBJECTIVES:**

Discuss sponsor's questions in briefing document dated May 18, 2000.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. Since there are numerous options for study designs, does the Division agree with the proposed design?

**FDA RESPONSE:**

- The Division agrees with the study design of a three armed randomized trial using oxaliplatin, versus oxaliplatin plus infusional 5-FU/LV versus infusional 5-FU/LV as the regimens. The primary endpoint would be survival with response rate as a secondary endpoint.

2. Does the Division agree with the proposed response rate analysis to potentially support conditional approval if a significant difference is demonstrated with 5-FU/LV + oxaliplatin?

**FDA RESPONSE:**

- Yes, the FDA agrees with response rate as a surrogate that may support conditional approval for second line therapy in patients with colorectal cancer who have relapsed less than 6 months following CPT-11 and 5-FU/LV. The NDA should not be submitted until all patients have been enrolled. The results should demonstrate a response rate that is clinically meaningful as well as showing a statistically significant difference over control. Approval determination would still be dependent upon a risk-benefit analysis.

3. Does the Division agree that this proposed study would support full approval of the claim, "Eloxatine™ (oxaliplatin) is indicated for patients with advanced colorectal cancer who have progressed on first-line 5-FU/LV + CPT-11"?

**FDA RESPONSE:**

- Yes, the proposed study could support full approval if a meaningful difference in survival were demonstrated.

***SPONSOR CLARIFICATION REQUEST:***

**Due to the availability of oxaliplatin in the U.S. Compassionate Use study (LTS 7072A), do you have any advice on how to address the potential impact of crossovers to oxaliplatin on the 3-arm study?**

**FDA Response:**

- FDA to discuss internally and forward response to Sanofi at a later date.

4. **Would the Division require an additional study in this patient population or another patient population to support full approval?**

**FDA RESPONSE:**

- The FDA would highly recommend an additional study to support any conclusions. An alternative additional study could be designed to enroll patients that had received 5-FU/LV as initial therapy for metastatic colorectal cancer and would randomize patients to either CPT-11 or CPT-11 plus oxaliplatin.

***SPONSOR STATEMENT:***

Sanofi-Synthelabo is committed to performing an additional study. Sanofi-Synthelabo will submit a proposed study design and synopsis within 4-6 weeks for discussion at a future meeting or teleconference.

5. **Would the Division consider inclusion of patients who have been only previously treated with 5-FU/LV + CPT-11 for metastatic disease?**

**FDA RESPONSE:**

- Yes, but the question requires explanation.

***SPONSOR CLARIFICATION AND QUESTION:***

The sponsor asked this question to determine FDA's position regarding patients who have relapsed less than 6 months following adjuvant therapy with 5-FU/LV + CPT-11. Based on discussions with external experts, Sanofi-Synthelabo proposes to exclude these patients. **Does the FDA agree with this proposal?**

**FDA RESPONSE:**

- Yes.

6. **Does the Division agree that clinically adjudicated progression (no scan documentation for submission) on prior therapy is adequate for enrollment to this Phase III randomized study?**

**FDA RESPONSE:**

- No, all patients who are enrolled should have scans documenting the previous response and the relapse.

***SPONSOR CLARIFICATION REQUEST:***

**Previous response:**

The proposed randomized study inclusion criteria do not include previous response.

**a. Why does the FDA want this information collected?**

**FDA RESPONSE:**

- Sponsor to submit protocol for FDA review and comment.
- b. If this information is needed, will documentation on the CRF of best response with the method of determination and date be considered adequate?**

**FDA RESPONSE:**

- Sponsor to submit protocol for FDA review and comment.
- c. If FDA will require collection of the scans, will FDA also require submission of these scans for review?**

**FDA RESPONSE:**

- Sponsor to submit protocol for FDA review and comment.

**Relapse or progression:**

- d. Will FDA require scans to be collected, or will documentation on the CRF of the relapse or progression with method of determination and date be considered adequate?**

**FDA RESPONSE:**

- No. Documentation on the CRF will be adequate.
- e. If FDA will require collection of the scans, will FDA also require submission of these scans for review?**

**FDA RESPONSE:**

- N/A

7. Based on the table above, what studies and data would be required to support conditional approval of this product in a specific patient population who have progressed after 5-FU/LV + CPT-11 or after second-line CPT-11?

**FDA RESPONSE:**

- The 3-arm randomized study may be adequate by itself to support accelerated approval. Regarding studies EFC 2970 and LTS 7072, see the response to question #9.

8. What kind of labeling indication would this support?

**FDA RESPONSE:**

- Labeling would be for an indication based on the population studied. Accelerated approval labeling would state that the approval is based on a surrogate marker (response rate) and that clinical benefit has not been demonstrated.

9. If studies EFC2970 and LTS7072 are only supportive of conditional approval and/or full approval, would documentation of prior therapy and response to prior therapy still be required?

**FDA RESPONSE:**

- All patients submitted to support an approval, whether accelerated or standard, should have full information that includes the initial regimen with doses and dates, the response to the initial regimen, the last date of therapy, and documentation of the date, sites and measurements of relapse.

***SPONSOR CLARIFICATION REQUEST:***

In the fax dated April 4, 2000, FDA raised the question regarding the 5-FU holiday and the ability to interpret the results from EFC2970 and LTS 7072.

- a. Does FDA still consider this a concern?

**FDA RESPONSE:**

- Yes.

- b. Would FDA ever consider these studies as the basis of a claim in patients who have progressed on first-line 5-FU/LV and subsequent second-line CPT-11?

**FDA RESPONSE:**

- No. Data collection not necessary since these studies will not be used to support the claim.

- Consider a study for single-agent to demonstrate benefit in third-line patients. Response and symptom improvement would be acceptable endpoints.

**ADDITIONAL STATISTICAL COMMENTS**

- All analyses should be based on ITT principles and include all patients as randomized.
- Fisher's exact test should be used in comparing response rates. The unadjusted log-rank tests should be used in comparing survival.

***SPONSOR REQUEST FOR CLARIFICATION:***

**Would the Agency agree to a log rank test, stratified for prognostic factors that are also used as strata in the treatment allocation, as the primary analysis?**

**FDA RESPONSE:**

- Yes. (Based on FDA's review of the protocol- to be submitted by sponsor).
- Please clarify what value for median survival of the oxaliplatin alone arm was used (8 months or 11 months) for sample size calculations. Conflicting information on this median survival time was submitted in sections 1.1 and 2.4.

***SPONSOR CLARIFICATION:***

**The oxaliplatin single agent median survival estimate is 8 months, the 5-FU/LV is 8 months, and the 5-FU/LV + oxaliplatin is 11 months. Sample size calculations were based on these median survival estimates.**

- Should both experimental arms win in their comparisons with the control arm (with respect to survival at final analysis or response rate at interim analysis), these experimental arms will need to be compared with a closed test procedure- a one-sided 0.05 level test having an alternative hypothesis that the combination arm is superior.

**SPONSOR'S ADDITIONAL QUESTIONS FOR DISCUSSION**

**10. Does the FDA agree to the submission of scans documenting responders only?**

**FDA RESPONSE:**

- No scans needed.



## MEETING MINUTES

**DATE:** May 12, 2003      **TIME:** 2:00 pm      **LOCATION:** Conference Room G

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 04-15-03

**FDA Response Date:** 04-16-03

**Briefing Document Submission Date:** 04-15-03

**Additional Submission Dates:** 05-06-03

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo, Inc.

### TYPE of MEETING:

1. Pre-sNDA: Presentation of efficacy data
2. Proposed Indication: Second-line treatment of metastatic colorectal cancer and adjuvant treatment of colorectal cancer

### FDA PARTICIPANTS:

Dr. Richard Pazdur, Director (Pre-meeting only)  
Dr. Grant Williams, Deputy Director  
Dr. John Johnson, Clinical Team Leader  
Dr. Amna Ibrahim, Clinical Reviewer  
Dr. Mark Rothmann, Statistical Reviewer  
Dr. Lilia Talarico, Associate Director (Pre-meeting only)  
Dr. Haripada Sarker, Chemistry Reviewer (Industry meeting only)  
Dr. Leigh Verbois, Pharm/Tox Reviewer (Industry meeting only)  
Patricia Delaney, Associate Director, Cancer Liaison Program, OSHI (Industry meeting only)  
Susan Daugherty, Consumer Safety Officer (Pre-meeting observer only)  
Christy Cottrell, Consumer Safety Officer

### INDUSTRY PARTICIPANTS:

Mark Moyer, Senior Director, Regulatory Affairs  
Dr. Nathalie LeBail, Senior Director, Clinical Oncology  
Dr. Sunil Gupta, Senior Director, Clinical Development  
Brenda Kozan, Regulatory Associate  
Franklin Vairinhos, Assistant Director, Regulatory Affairs  
Dr. Brent Burger, Senior Statistician II  
Dr. Lania Boudiaf, Medical Manager  
Dr. Alain Herrera, Head of Oncology Business Unit  
Dr. Robert Bigelow, Biostatistics  
Dr. J.P. Bizzari, Vice President, Clinical Oncology  
Dr. Sylvain Durrleman, Head of Biostatistics  
Dr. Paul Juniewicz, Project Director  
Dr. Meg Mooney, NCI/CIB Senior Investigator

## **BACKGROUND:**

Eloxatin™ (oxaliplatin) for Injection was approved on August 9, 2002, for use in combination with infusional 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.

The purpose of this meeting was to present to the FDA the results for two studies: EFC4584 which is the study on which the accelerated approval was based and the MOSAIC study which is a Phase 3 study in adjuvant treatment of colon cancer. Abstracts for these studies were submitted to the American Society of Clinical Oncology (ASCO) and were accepted for oral presentation during the 2003 ASCO meeting.

The sponsor submitted two general questions for discussion, which are listed below with FDA responses. However, the meeting was primarily a sponsor presentation and the slides are attached.

## **QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

- 1. Final efficacy analysis of EFC4584 demonstrated a statistically significant result for Eloxatin (oxaliplatin) + 5-FU/LV for response rate, and time to progression. The final overall survival analysis demonstrated a trend without statistical significance for the stratified log rank test of Arm A vs. C. Does the FDA have any recommendations regarding this study and the study analyses?**

### **FDA RESPONSE:**

- We do not have any recommendations. We await the submission of other confirmatory trials, such as the MOSAIC trial and the NCCTG N9741.
- 2. The MOSAIC study's primary endpoint is a 3-year Disease Free Survival; does the FDA consider this endpoint appropriate to support potential approval of an adjuvant claim in colorectal cancer?**

### **FDA RESPONSE:**

- To this date, all approvals in this indication have been based on overall survival. We will be discussing cancer endpoints in workshops and with ODAC over the coming year.
- Please clarify whether you are continuing to gather data on overall survival.

**ADDITIONAL COMMENTS**

- How many patients had missing data (missing CT scans) for TTP on your final analysis?
- What were the results of RR and TTP from the independent review? You have submitted the investigator results.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

**ACTION ITEMS:**

1. Sponsor to submit copies of all slides shown during the presentation. **DONE- Mark Moyer- 5/12/03.**

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Clinical Reviewer

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

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

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Amna Ibrahim  
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## INTERNAL MEETING MINUTES

**DATE:** May 7, 2003      **TIME:** 9:30 am      **LOCATION:** Conference Room A

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 03-28-03

**FDA Response Date:** 04-09-03

**Briefing Document Submission Date:** 03-28-03

**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo, Inc.

### **TYPE of MEETING:**

1. Pre-sNDA content meeting
2. Proposed Indication: First-line colorectal cancer

**FDA PARTICIPANTS:** Dr. Grant Williams, Deputy Director  
Dr. John Johnson, Clinical Team Leader  
Dr. Amna Ibrahim, Clinical Reviewer  
Dr. Mark Rothmann, Statistical Reviewer  
Dr. Lilia Talarico, Associate Director  
Susan Daugherty, Consumer Safety Officer (Observer only)  
Christy Cottrell, Consumer Safety Officer

### **BACKGROUND:**

Eloxatin™ (oxaliplatin) for Injection was approved on August 9, 2002, for use in combination with infusional 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.

The Division met with the sponsor on January 13, 2003, for a Pre-sNDA meeting during which the results of the NCCTG study N9741 were reviewed and discussed. During the meeting, the sponsor indicated that they would be following up with the FDA with specific questions concerning the content of the upcoming sNDA for the first-line treatment of advanced colorectal cancer. This is the referenced follow-up meeting.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**1. Electronic sNDA Submission**

- a. Will the Division accept the electronic submission as both the archival copy and the review copy of the application, i.e., no paper documents will be provided with the exception of those requiring original signatures?

**FDA RESPONSE:**

- A paper copy of the Study Report should be submitted.

- b. Additionally, Sanofi-Synthelabo intends to provide Desk Copies containing the cover letter, sNDA Table of Contents, and the Item 3 Summary Document in paper format. How many copies does the Division request?

**FDA RESPONSE:**

- Please provide 10 desk copies in addition to the standard number of reviewer copies.

**2. Pivotal clinical study report (CSR) content**

Because the electronic database for EFC7462/N9741 will be submitted, Sanofi-Synthelabo proposes not to include the following CSR appendices described in the ICH E3 CSR guideline: patient data listing (16.2.1 – 16.2.8) and individual patient data listings (16.4). Does FDA agree that this is acceptable?

**FDA RESPONSE:**

- This is acceptable.

**3. Ancillary first-line studies**

- a. If FDA requests a paper review copy for the sNDA (see Question 1.a), then Sanofi-Synthelabo proposes to provide just the EFC2962 and EFC2961 study reports in electronic format only, i.e., without accompanying paper review copies. Does FDA find this acceptable?

**FDA RESPONSE:**

- Please provide paper copies of study reports for EFC2962 and EFC2961.

- b. **The electronic databases for EFC2961 and EFC2962 were previously submitted in the June 2002 NDA (No. 21-492). Does FDA want these same databases to be re-submitted in the sNDA?**

**FDA RESPONSE:**

- Yes.

**4. Summary documents**

- a. **In lieu of an ISE, Sanofi-Synthelabo proposes to provide a side-by-side tabular presentation of survival, PFS, and response rate for the 2 completed randomized first-line studies utilizing the FOLFOX4 regimen (EFC7462/N9741 and EFC2962). In addition, a tabular presentation of efficacy for the 3 randomized first-line studies with other regimens (EFC2961, LIFE, and EFC7233) will also be provided. These displays will be provided as part of the Background/Overview of Clinical Investigations section of Item 8, and will support marketing approval and labeling. Does FDA agree that this is acceptable?**

**FDA RESPONSE:**

- Yes.
  - For time to event endpoints, the sponsor should submit the number of events in each arm, the estimates of the log-hazard ratio and the corresponding standard error. Any estimate that is submitted should be accompanied by its corresponding standard error or a corresponding confidence interval. Any estimate of a median should be accompanied with a confidence interval based on non-parametric procedures that do not any make normality assumptions.
- b. **In lieu of an ISS, Sanofi-Synthelabo proposes to provide safety tables of all AEs for the completed randomized studies utilizing the FOLFOX4 regimen (EFC7462 and EFC2962). These displays would be provided as part of the Background/Overview of Clinical Investigations section of Item 8, and will establish that EFC7462 is sufficient to support safety labeling. Does FDA agree that this is acceptable?**

**FDA RESPONSE:**

- Yes. Please include all safety data from any studies using the FOLFOX4 regimen in any indication.

- c. In lieu of the risk/benefit and clinical data summary portions of Item 3, Sanofi-Synthelabo proposes to provide the main body of the EFC7462 study report (no appendices). Does FDA agree that this is sufficient for Item 3 of the sNDA?

**FDA RESPONSE:**

- Yes.

- d. Since the EFC7462 CSR provides the pivotal safety and effectiveness information for the first-line indication, does FDA agree that the Integrated Summary of Benefits and Risks portion of Item 8 is not necessary?

**FDA RESPONSE:**

- Yes.

**5. CRFs and Patient Narratives**

- a. Does FDA agree that CRFs and narratives can be limited to the treatment arm of interest in EFC7462 (FOLFOX4)?

**FDA RESPONSE:**

- Yes. However, if requested, you should make other CRFs/narratives available to the Agency.

- b. Does the FDA find the CRF proposal acceptable?

**FDA RESPONSE:**

- See above.

- c. Does the FDA find the narrative proposal acceptable?

**FDA RESPONSE:**

- See above.

**6. Safety update**

As agreed with the FDA for the second-line NDA (No. 21-492), Sanofi-Synthelabo proposes to submit the 4-month safety update in the same format as the IND annual report with safety data provided for the additional reporting period, i.e., cumulative data would not be provided. Does FDA find this safety update proposal acceptable?

**FDA RESPONSE:**

- Yes.

These responses were faxed to the sponsor on May 7, 2003. After reviewing these comments, the sponsor chose to cancel the teleconference that was scheduled for May 15, 2003.

\_\_\_\_\_  
Christy Cottrell  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Clinical Reviewer

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Amna Ibrahim  
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## MEETING MINUTES

**MEETING DATE:** January 13, 2003      **TIME:** 2:00 pm      **LOCATION:** G

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 11-14-02

**Briefing Document Submission Date:** 12-13-02

**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### TYPE OF MEETING:

1. Pre-sNDA
2. **Proposed Indication:** First line colorectal cancer

### FDA PARTICIPANTS:

Dr. Grant Williams, Deputy Director  
Dr. Martin Cohen, Medical Team Leader  
Dr. Amna Ibrahim, Medical Officer  
Dr. Gang Chen, Statistical Team Leader (Pre-meeting only)  
Dr. Mark Rothmann, Statistical Reviewer  
Dr. Atik Rahman, Biopharmaceutics Team Leader (Industry meeting only)  
Dr. Brian Booth, Biopharmaceutics Reviewer (Pre-meeting only)  
Dr. Steven Hirschfeld, Medical Officer (Industry meeting only)  
Dr. Kate Phelan, Safety Evaluator, ODS  
Joann Minor, Associate Director, Cancer Liaison Program, OSHI  
Sallie Forman, Patient Representative  
Christy Cottrell, Consumer Safety Officer

### INDUSTRY PARTICIPANTS:

Dr. Robert Bigelow, Biostatistics  
Dr. Jean-Pierre Bizzari, Clinical Development  
Dr. Sylvain Durrleman, Biostatistics  
Dr. Sunil Gupta, Clinical Development  
Dr. Richard Gural, Regulatory Affairs  
Dr. Alain Herrera, Business Unit  
Dr. Paul Juniewicz, Project Direction  
Brenda Kozan, Regulatory Affairs  
Mark Mariani, Regulatory Affairs  
Mark Moyer, Regulatory Affairs  
Dr. Richard Goldberg, Study Chair, NCCTG  
Dr. Daniel Sargent, Statistician, NCCTG (by phone)  
Dr. Percy Ivy, NCI  
Dr. Margaret Mooney, NCI

### MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated December 13, 2002.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

- 1. Sanofi-Synthelabo plans to submit protocol-defined analyses for time to tumor progression and overall survival to demonstrate the efficacy of oxaliplatin. The endpoints of time to treatment failure and objective tumor response will also be presented, as defined in the protocol. The population for the primary analysis will consist of the 796 patients concurrently randomized to IFL (Arm A), FOLFOX4 (Arm F), or oxaliplatin + CPT-11 (Arm G). Does the Division require any of the following?**

**Analysis of additional endpoints;**

**Further analysis of protocol-defined endpoints;**

**Analyses of other populations, besides the patients concurrently randomized to Arms A, F or G?**

**FDA RESPONSE:**

- No additional endpoint analysis is required. No analyses of other populations, other than those of Arms A, F or G are required. However, comparison of overall survival, TTP, RR of reduced IFL to FOLFOX for patients accrued after 4/25/2001 through 4/25/2002 would be of interest.
- Include results from any interim analyses (looks).

*Discussion: The sponsor showed the slide titled, "N9741 Report Proposal". The Division agreed to review the sponsor's proposal and provide feedback within 2 weeks.*

- 2. The sponsor plans to submit the Data Monitoring Committee's minutes and decisions regarding N9741 in support of the sNDA. Sanofi-Synthelabo does not plan to submit data for patients entered onto arms that were dropped and/or modified during the course of the study. Does the Division agree?**

**FDA RESPONSE:**

- Yes. The study report should capture the reasons for protocol modifications that occurred during the course of the study.

*Discussion: The sponsor agreed.*

- 3. Study N9741 has demonstrated a significant improvement in overall survival, time to progression, response rate, and a positive risk/benefit for patients treated with first-line FOLFOX4 compared to IFL. Does the Division have any questions or suggestions regarding study N9741 as the pivotal study for potential approval of a first-line indication as an sNDA submission?**

**FDA RESPONSE:**

- There were several protocol modifications made. The amendments to the Statistical Analysis Plan need to be clearly outlined, including the dates when they were made.
4. **Due to the way neurotoxicity information was captured in study N9741, it is not possible to analyze neuropathy according to duration (acute  $\leq$  14 days vs. persistent  $>$  14 days) as is presented in the current Eloxatin labeling. In addition, the nature of the events was not captured in the study, therefore only overall neuropathy can be presented. Since Sanofi-Synthelabo and FDA's approach to overall neuropathy yielded similar results (see Slide 19, Comparison of Overall Neuropathy), does FDA agree that this will be sufficient for labeling?**

**FDA RESPONSE:**

- Yes.
- Please clarify how data was collected for neuropathy.

*Discussion: The sponsor showed the slide titled, "Neurotoxicity Grading – Protocol Page 55".*

5. **Based on the FDA's May 1998 guidance, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" (Section III.A.1.), would the FDA consider it acceptable to provide the NCCTG database plus a preprint (accepted for publication) in lieu of a study report to support review?**

**FDA RESPONSE:**

- No. Given the complexity of this case with dropped study arms and altered doses, we would prefer a study report.

**OTHER COMMENTS**

- Include results for survival, time to progression and tumor response rates for studies EFC 2961, EFC 2962, EFC 7233, and any other study that involves oxaliplatin in first-line metastatic colorectal cancer.
- In the protocol section of the background package, pages 26-32, how much of the data collected in the tables are actually recorded in the electronic database?

*Discussion: The sponsor showed the slides titled, "Randomized 1<sup>st</sup> Line SSR Studies" and "Other and Non-Randomized 1<sup>st</sup> Line Studies". The sponsor proposed to include only the randomized study information and the Division agreed. Regarding the second bullet, the sponsor clarified that anything in the CRF's is available in the electronic database, and other parameters noted in the study scheme that are not listed on the CRF are not included.*

**ACTION ITEMS:**

- FDA to review proposal for study pre-print and provide comments within 2 weeks. **DONE – CCOTTRELL – 1/23/03**
- Sponsor to submit copies of all slides shown during the meeting. **DONE – MMARIANI – 1/13/03**

There were no unresolved issues. The meeting concluded at 2:50 pm.

Concurrence Chair:

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

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/s/

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Christy Cottrell  
1/30/03 09:27:36 AM

Amna Ibrahim  
1/30/03 11:14:25 AM

## MEETING MINUTES

**MEETING DATE:** March 22, 2002      **TIME:** 2:30 pm      **LOCATION:** G

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 03-15-02

**Briefing Document Submission Date:** 03-15-02

**Additional Submission Dates:** 03-19-02 and 03-21-02

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### **TYPE OF MEETING:**

1. Pre-NDA guidance meeting
2. **Proposed Indication:** Colorectal cancer

### **FDA PARTICIPANTS:**

Dr. Richard Pazdur, Division Director  
Dr. John Johnson, Medical Team Leader  
Dr. Amna Ibrahim, Medical Reviewer  
Dr. Raji Sridhara, Statistical Reviewer (Acting Team Leader)  
Dr. Grant Williams, Deputy Director (Industry meeting only)  
Patricia Delaney, Assoc. Dir., Cancer Liaison Program, OSHI (Industry meeting only)  
Christy Wilson, Consumer Safety Officer

### **SPONSOR PARTICIPANTS:**

Mark Moyer, Director, Regulatory Affairs  
Dr. Sunil Gupta, Senior Director, Clinical Development, Oncology  
Dr. Carlos Garay, Director, Clinical Development  
Dr. Paul Juniewicz, Senior Director  
Dr. Nassir Habboubi, Vice President, Clinical Research  
Dr. Richard Gural, Vice President, Regulatory Affairs  
Dr. Robert Bigelow, Statistician, Oncology

### **MEETING OBJECTIVES:**

To review and discuss the positive results obtained from the ongoing oxaliplatin study EFC4584, and to discuss proposed timing of the NDA submission. To discuss sponsor's questions in the briefing document dated March 19, 2002.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

- 1. Based on the Statistical Analysis Plan, the endpoints submitted in the pre-meeting package are the only endpoints that Sanofi-Synthelabo plans to analyze for this NDA. Based on your review of these results are there any additional data displays or analyses that should be performed for inclusion in the NDA? Specifically, does the FDA want any further analysis of clinical benefit?**

**FDA RESPONSE:**

- The pre-specified analyses in the protocol regarding the clinical benefit assessment should be submitted. This includes pair-wise comparisons among the three treatment arms with the log rank test and analyses of clinical benefit comparing the three arms in terms of proportion of patients who are symptomatic at baseline and who show improvement while on treatment, using Fisher's exact test. Please submit survival data without comparative analysis.

**Discussion:** The following bullet was added after discussion:

- Submit survival data based on the cut-off date of December 18, 2001.
- 2. Sanofi-Synthelabo has had all scans digitally prepared and evaluated by an independent radiology group. Does the FDA want scans submitted for all responders based on the investigator and independent assessments?**

**FDA RESPONSE:**

- Yes.
- 3. Due to data collection and entry requirements for an ongoing study within Sanofi-Synthelabo, the database has data beyond the 18 December 2001 cut-off date. The data beyond the 18 December 2001 is incomplete, since it does not contain data for all patients or complete data for an individual patient. The 18 December 2001 cut-off date will be utilized for all data displays and analyses. Tumor measurements for confirmation of responders that became available after 18 December 2001 have been utilized for the response analysis and will be included in the database. Does the FDA agree with the approach for the data cut-off for data displays and analyses? Does the FDA have a preference on whether the additional data beyond 18 December 2001 remains in the database, or is removed from the database submitted with the NDA?**

**FDA RESPONSE:**

- Data after the cut-off date should not be submitted, unless it assists in confirming a response attained. This data should be provided for patients in all three arms. Please provide both confirmed and unconfirmed response rates up to December 18, 2001.
- In the electronic datasets, especially in table NEWL, where only the visit numbers are given, please give the dates of the visits as well.

**4. Will the FDA grant Fast-Track designation to this product to allow a rolling NDA submission?**

**FDA RESPONSE:**

- Yes.
- Please be reminded that all pre-submissions must be complete, reviewable sections of the NDA.

**Discussion:** The sponsor explained that the clinical data would be ready for submission shortly. However, the Integrated Summary of Safety was the rate-limiting factor in submitting the complete clinical section of the NDA. The Division agreed to check with Randy Levin about whether the Division could accept the clinical data early (before the ISS was completed) as an incomplete clinical section of the rolling NDA. The Division also agreed to follow-up on a comprehensive Table of Contents for the electronic NDA.

**OTHER COMMENTS**

- As a reminder, User Fees will need to be paid for this NDA, since it provides for a new indication with new, unreviewed clinical data.
- In order to facilitate a timely review, it is suggested that questions can be sent to Sanofi-Synthelabo by e-mail (secure, if necessary), with responses sent back to the reviewer by the same route. All e-mails must be copied to the Project Manager.
- Is the NDA submission still planned for June 2002?

**Discussion:** The sponsor confirmed that the last section of the rolling NDA submission was still planned for June, with several sections of the NDA ready for submission immediately.

**ACTION ITEMS:**

- FDA to check with Randy Levin about whether the Division could accept the clinical data early (before the ISS was completed) as an incomplete clinical section of the rolling NDA. **DONE: Grant Williams- 3/26/02. The Division will accept the clinical data early as an incomplete clinical section of the rolling NDA.**
- FDA to follow-up on a comprehensive Table of Contents for the electronic NDA. **DONE: Christy Wilson- 3/28/02. The sponsor may not re-submit already submitted sections of the NDA with a comprehensive, hyper-linked Table of Contents. Each section of the rolling NDA should have its own Table of Contents, and may reference the date of submission of previous sections of the NDA instead of hyperlinking to those previous submissions.**

- Sponsor to request Fast Track designation and an NDA number prior to submission of the first section of the rolling NDA.
- Sponsor to submit tradename for preliminary review as soon as possible.
- Sponsor to provide a plan for compassionate use and for patients receiving oxaliplatin alone.

There were no unresolved issues. The meeting concluded at 4:00 pm.

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Christy Wilson  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

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/s/

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Christy Wilson

4/2/02 08:05:00 AM

Draft minutes signed by RSridhara on 3-29-02; by AIbrahim  
on 4-1-02

Amna Ibrahim

4/2/02 10:41:01 AM

## MINUTES OF TELECONFERENCE

**MEETING DATE:** January 28, 2002      **TIME:** 12:00 pm      **LOCATION:** A

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** by email on 01-11-02  
**Briefing Document Submission Date:** by email on 01-11-02  
**Additional Submission Dates:** N/A

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### TYPE OF MEETING:

1. Other- Clarification of comments from Pre-NDA logistics meeting
2. **Proposed Indication:** Colorectal cancer

### FDA PARTICIPANTS:

Dr. Richard Pazdur, Division Director  
Dr. John Johnson, Medical Team Leader  
Dr. Amna Ibrahim, Medical Reviewer  
Dr. Gang Chen, Statistics Team Leader  
Dr. Mark Rothmann, Statistics Reviewer  
Joann Minor, Associate Director, Cancer Liaison Program, OSHI  
Christy Wilson, Consumer Safety Officer

### SPONSOR PARTICIPANTS:

Remi Castan, Clinical Research  
Nassir Habboubi, Clinical Research  
Carlos Garay, Clinical Research  
Sunil Gupta, Clinical Research  
Brent Berger, Biostatistics  
Bob Bigelow, Biostatistics  
Tom Guinter, Clinical Information Systems  
Mark Mariani, Drug Regulatory Affairs  
Mark Moyer, Drug Regulatory Affairs

### MEETING OBJECTIVES:

To provide clarification on specific comments made during the Pre-NDA logistics teleconference held on December 18, 2001.

### BACKGROUND INFORMATION:

The sponsor sent the following information to the Division by e-mail on January 11, 2002 in preparation for this teleconference.

Databases - We did not make a specific proposal; therefore, we are not certain how to interpret your statement that the proposal is fine. Our proposal would be to include: EFC4584 study database as one dataset and the ISS database (as originally formatted) from the previously withdrawn NDA as another dataset. This would provide the safety data requested. The ISS database has datafield names that sometimes are not exactly the same names as in the EFC4584 database, but maintaining the database in the current format ensures that the programs utilized by both Sanofi-Synthelabo and FDA previously will still run properly. There are also some other differences that make it seem more appropriate to maintain the current ISS database as it currently exist, and separate from the EFC4584 database. Details of these differences can be discussed during the teleconference.

Time Related Efficacy Parameters - Please clarify if the request for analysis of these parameters if 50% of the patients have an event is for the 450 patients in the response rate analysis, or the overall study population of around 786 patients. Please also clarify which parameters that FDA would like included. It would be helpful to specifically discuss FDA's expectations during a teleconference, since Sanofi-Synthelabo is willing to provide what is requested.

#### DISCUSSION:

*Regarding the Databases:* The Division stated that the format used in the previous NDA submission was acceptable and preferred. The Division asked whether the sponsor was planning to submit a pooled analysis as well. The sponsor said that it would be difficult to match the different grading systems, but that they plan to provide a representation of all studies. They further explained that the study report databases would include more information, and would be comprehensive by study. The Division requested that all information be submitted with the NDA.

*Regarding the Time-Related Efficacy Parameters:* The Division explained that the 50% is out of the number of patients that are relative to the particular endpoint. The Division reminded the sponsor that they are to submit to the FDA the same data that is sent to the Data Safety Monitoring Board. The Division further clarified that if the sponsor has 50% of the patients, they should do an analysis. If they have less than 50% of the patients, they should not do an analysis, but the Division still wants to see the information.

The sponsor informed the Division that they anticipate submitting the NDA in June 2002.

There were no action items or unresolved issues. The meeting concluded at 12:45 pm.

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

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/s/

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Christy Wilson

2/19/02 11:50:00 AM

Draft minutes signed by A Ibrahim on 2-12-02 and by

MRothmann on 2-13-02

Amna Ibrahim

2/20/02 04:16:40 PM

## INTERNAL MEETING MINUTES

**MEETING DATE:** December 11, 2001    **TIME:** 12:30 pm    **LOCATION:** B

**IND/NDA:** IND 41,817

**Meeting Request Submission Date:** 10-24-01  
**Briefing Document Submission Date:** 11-19-01  
**Additional Submission Dates:** 12-17-01 (fax)

**DRUG:** Oxaliplatin

**SPONSOR/APPLICANT:** Sanofi-Synthelabo

### TYPE OF MEETING:

1. Pre-NDA logistics meeting
2. **Indication:** Colorectal cancer

**FDA PARTICIPANTS:** Dr. Richard Pazdur, Division Director  
Dr. John Johnson, Clinical Team Leader  
Dr. Amna Ibrahim, Clinical Reviewer  
Dr. Chengyi Liang, Chemistry Reviewer  
Dr. Gang Chen, Statistics Team Leader  
Dr. Mark Rothmann, Statistics Reviewer  
Dr. Brian Booth, Biopharmaceutics Reviewer  
Dr. Lilia Talarico, Detail, Special Assistant to the Director  
[  
Christy Wilson, Consumer Safety Officer

### MEETING OBJECTIVES:

As identified by the sponsor in the background package dated November 19, 2001, the meeting objectives are:

- Review previous written agreements to ensure clarity
- Gain concurrence on data to support the response rate analysis, including safety and efficacy, to support proposed regimen
- Gain concurrence on NDA content and a proposal to limit the number of overlapping summary documents, since this NDA will be based on one study, EFC4584
- Review of a mock Item 11 electronic submission, including data for 3 representative EFC4584 patients
- Review patient profile content for ease of review
- Electronic archival submission: timing, content, format
- Review of overall NDA timing

### QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The questions were divided into sections. The section titles precede the questions.

**PREVIOUS WRITTEN AGREEMENTS**

1. Does the Division have any further clarifications that should be made to ensure agreement?

**FDA RESPONSE:**

- You are referred to the correspondence exchanged since the submission of the initial protocol.
- Regarding Sanofi's submission 343 dated March 9, 2001, which addressed the comment in Item #3, we would like to clarify that the statistician had found your proposal acceptable and had no additional comments.

**NDA CONTENT**

1. Does the Division agree with the proposed studies for submission in Item 8 of this NDA as outlined in the NDA Content Proposal document (Appendix 1)?

**FDA RESPONSE:**

- Inclusion of scientific rationale and purpose will be required. The omissions suggested are otherwise acceptable. Safety datasets and study reports for EFC2961, 2964 and 2962 should be submitted.

2. Does the Division agree that individual patient data listings do not need to be included in the EFC4584 study report since the electronic database and patient profiles will be provided in Item 11 of the NDA?

**FDA RESPONSE:**

- Yes.

3. Does the Division agree with the proposal to omit or substitute the overlapping summaries contained in NDA Items 3 and 8 as outlined in the NDA Content Proposal document (Appendix 1)?

**FDA RESPONSE:**

- No. Item 3.2: Scientific rationale and purpose will be required.

4. Does the Division agree with the proposed approach for presenting safety and efficacy in the package insert?

**FDA RESPONSE:**

- Yes. The safety databases from EFC 2961, 2962 and 2964 should be submitted.

5. Does the Division agree with the proposal for the Integrated Safety Summary (ISS) to support this NDA?

**FDA RESPONSE:**

- Yes. Please confirm that the cut off date for safety in the NDA will be 12-18-01.

**DATA TO SUPPORT NDA**

1. Does the Division agree with Sanofi-Synthelabo's proposed data cut-off and the plan for handling late-occurring responses (CR and PR) to support an NDA based on the response rate analysis?

**FDA RESPONSE:**

- Yes. Also, individual tumor measurements must be submitted to verify the investigator evaluations.

2. Does the Division anticipate additional requests for updated data during the review?

**FDA RESPONSE:**

- No further requests are anticipated at this time for updated data.

3. If yes, is there any particular data parameter the Division would like to see?

**FDA RESPONSE:**

- N/A.

4. Does the Division want the survival and other secondary time-related parameters summarized in the EFC4584 response rate report?

**FDA RESPONSE:**

- If the sponsor has looked at the survival data, the significance level for the final analysis needs to be adjusted appropriately. Any analyses performed either on survival or on any secondary endpoint need to be submitted with the NDA.

**ITEM 11 ELECTRONIC SUBMISSION**

- 1. Are the content and format of the efficacy/safety datasets intended for submission adequate to support the Division's review of EFC4584?**

**FDA RESPONSE:**

- Yes.
- We should receive all raw datasets for each individual patient.
- Please provide definitions for rows, columns, and table content.

- 2. Does FDA find that the documentation provided for the EFC4584 database is adequate?**

**FDA RESPONSE:**

- Yes.

- 3. Does the Division have any comments on the patient profiles intended for submission in the NDA?**

**FDA RESPONSE:**

- These appear helpful. However, please provide a decode for various headings (at the time of submission of the NDA) in order to clarify certain points:
  - For example, why is the 'End date of Saltz to randomization' a number and not a date?
  - Do 'Days from last dose to off-study' pertain to the prior Saltz regimen or the current study drugs?
  - Do the numbers in the AE columns pertain to the grade of AE?

**ITEM 11 ELECTRONIC SUBMISSION- HUMAN PK DATA**

- 1. Is the content and format of the PK database intended for submission adequate to support the Division's review of human pharmacokinetics?**

**FDA RESPONSE:**

No. Please make the following additions/corrections/inclusions:

- Include the creatinine clearances for each patient in the electronic databases.

- Include the plasma concentration of 5-FU and demographic data for the patients/subjects in studies INT 3681 and INT 3682 in the electronic database.
  - Include the in vivo biotransformation data for study PKM2983, part 1 in the electronic database.
2. Does FDA find that the documentation adequately describes the database?

**FDA RESPONSE:**

- Yes.

**ELECTRONIC ARCHIVAL PROPOSAL**

1. Does the Division agree that the electronic archival copy can also serve as the review copy, i.e., no paper documents will be submitted except those requiring an original signature?

**FDA RESPONSE:**

- No. See #2 below.
2. If FDA requires a paper review copy, Sanofi-Synthelabo will submit a paper review copy of the portions of the technical sections, as required in the 1999 electronic submission guidance, for Items 4, 5, 6, and 8. If Sanofi-Synthelabo opts to make a pre-submission, does the Division agree that the paper review copy of the pre-submission does not need to be provided again at the time of the complete NDA submission?

**FDA RESPONSE:**

- In addition to Items 1, 2, and 3, and the technical sections of the NDA identified above, the reviewers have identified the following items that they request be submitted in paper form:

Clinical – Items 11, 12, and all study reports. (Only CRF's for SAE's and deaths need to be submitted)

Clinical Pharmacology – All study reports.

Statistics – Reports of all analyses.

- You will not be required to resubmit these if submitted prior to the complete NDA submission.

3. For FDA's convenience, Sanofi-Synthelabo will provide paper desk copies of the Item 3 NDA Summary and CDs containing the line-numbered proposed labeling document in Microsoft Word.

a. How many paper desk copies of the Item 3 NDA Summary does the Division require?

**FDA RESPONSE:**

- Please submit 15 desk copies of the NDA Summary volume.

b. Which version of Microsoft Word is currently being used in the Division?

**FDA RESPONSE:**

- Word 95 and 97.

c. How many CDs containing the line-numbered proposed labeling does the Division require?

**FDA RESPONSE:**

- One- submitted to the Project Manager.

4. Does the Division require the 3 review copies of the CMC analytical methods validation, and 4 review copies of the draft labels and labeling?

**FDA RESPONSE:**

- The CMC section should include the information of analytical method validation. However, the finalized method validation package is submitted just after the approval of an NDA (one copy is for the review Division and the other two copies are for FDA laboratories).

**NDA TIMING**

1. Will the Division accept the 4-month safety update as the safety submission required at approval?

**FDA RESPONSE:**

- Complete safety data will be required at the time of NDA submission. 4- month safety update will be acceptable as part of the safety submission for accelerated approval. For an accelerated approval, we need the safety update at 3 months.

## **OTHER COMMENTS**

### **NDA/sNDA Presentations to CDER's Division of Oncology**

- The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

### **Financial Disclosure Final Rule**

- We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

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

### **Pediatric Final Rule**

- Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to <http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>.

### **Pediatric Exclusivity**

- Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if Oxaliplatin is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Request (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "*Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act*" at Drug Information Branch (301) 827-4573 or <http://www.fda.gov/cder/guidance/index.htm>. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at <http://www.fda.gov/cder/guidance/3756dft.htm>.

The Division faxed responses to the sponsor on December 11, 2001. The sponsor then sent "Requests for Clarification" back to the Division on December 17, 2001. However, the Division determined that more time would be needed to review some of the clarification questions. The Division agreed to answer the clarification requests as soon as possible and fax the responses to the sponsor. The "Requests for Clarification" are listed below.

### CLARIFICATIONS

1. **Sanofi-Synthelabo has safety databases for individual studies EFC2961, 2964 and 2962, as well as an Integrated Summary of Safety (ISS) database containing safety data for all three studies. In the integrated database some adverse events and pre-listed toxicities have been recoded to ensure consistency for pooling of data. The primary study EFC4584 safety database is in a different format, which is more in agreement with FDA's ESUB guidance. Can the FDA provide further details on what datasets the Agency would like to receive in the NDA submission?**

#### **FDA RESPONSE:**

[DEFERRED]

2. **Sanofi-Synthelabo has been asked by the EFC4584 independent data safety monitoring committee (DSMC) to provide statistical analysis of the primary survival endpoint and other time-related endpoints prior to the NDA submission. These analyses would be confidential and would be known only to an in-house statistician and the DSMC. Persons involved with the conduct of the study will not see these analyses. Sanofi-Synthelabo is of the opinion that providing these analyses to the DSMC does not inflate the type I error and will not require adjustment in the final analysis. Does the FDA concur? Does the FDA want any analyses of time-related parameters [ (1) Time to Symptom Worsening (TTSW), (2) Time to Progression (TTP), (3) overall survival, etc] submitted in the NDA, or will response rate alone with safety and dosing information be sufficient? Does FDA want calculated time-related parameters to be included on the database for individual patients, even if no analysis is done?**

#### **FDA RESPONSE:**

[DEFERRED]

3. Sanofi-Synthelabo proposes to fulfill FDA's request for in vivo biotransformation data for study PKM2983, part 1 by providing the percentage of platinum for each of the separated metabolites in plasma and urine on a per subject basis. Where available, the identity of the component will be provided. Also to be included will be the standard demographic information on these patients as given in the other ESub data sets. Does FDA agree that this represents the data request?

**FDA RESPONSE:**

- Yes.

4. Regarding the NDA Esub, Sanofi-Synthelabo would like to clarify the intended format of the submission contents. We propose to submit the archival NDA copy as a fully electronic submission in accordance with the 1999 Guidance for Industry, "Providing Regulatory Submissions in Electronic Format - NDAs". In addition, we propose to provide a full paper review copy of all Items with the exception of Item 11 (CRTs) and Item 12 (CRFs). These items will be provided in full in the electronic submission. [Please note that per the Esub Guidance the paper review copy of Item 10 (Statistical) will be a duplicate of Item 8, but jacketed for the statistician.]

**FDA RESPONSE:**

[DEFERRED]

5. Additionally, per your request, 15 desk copies of the NDA Summary volume will be submitted along with a CD containing the line-numbered proposed labeling document.

Does the Division find the clarification above acceptable?

- Yes.

Other than the "Requests for Clarification" listed above, the sponsor felt no further discussion was needed and cancelled the teleconference scheduled for December 18, 2001.

The internal meeting concluded at 1:15 pm.

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

Concurrence Chair:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

### ADDENDUM TO MEETING MINUTES

In response to the "Requests for Clarification," the Division forwarded the following comments to the sponsor by facsimile transmission on December 21, 2001.

1. The safety databases as proposed are acceptable.
2. Regarding time to event endpoints, the FDA would like this information submitted for each individual patient. If more than 50% of the patients have had an event, a statistical analysis should be submitted. If patients, investigators and Sanofi are still blinded to this information, the FDA will make every effort not to disclose it publicly, e.g., in relation to a Public Advisory Committee meeting.

If a statistical analysis is done for the DSMC, a statistical adjustment must be made for subsequent analyses.

3. The proposal regarding the e-submission is acceptable.

\_\_\_\_\_  
Christy Wilson  
Consumer Safety Officer

concurrence:

\_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Officer

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/s/

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Christy Wilson  
1/11/02 11:04:33 AM

Amna Ibrahim  
1/24/02 01:51:32 PM

7 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Muhammad Salim, M.D.  
Allan Blair Cancer Centre, Pasqua Hospital,  
4101 Dewdney Ave  
Regina, Saskatchewan  
S4T 7T1 Canada

Dear Dr. Salim,

Between December 7 and December 12, 2003, Ms. Nancy Bellamy and Dr. David Gan, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation NDA 21492/SR96669, titled 'A Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL / Eloxatin), 5-Fluorouracil (5-FU), and Irinotecan (CPT-11) as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum'. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Ballamy presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge your discussion with the inspector, Ms. Ballamy, December 11, 2003, responding to the Form FDA 483. We wish to emphasize the following:

- 1) You did not follow the protocol (483 items 2 (a, b, and c)
  - a. The protocol required that subjects must meet the inclusion criteria to be enrolled into the study. subject #92830/9027596 did not meet inclusion criteria in that he had uncontrolled hypertension and was enrolled in the study.
  - b. The protocol required that subjects be terminated from the study if patients show progression of the disease. Subject # 91091/9026955 was not terminated from the study as required by protocol when he had progression of disease. A new lesion was detected by CT scan.
  - c. The protocol required that subjects to receive right study drug dose. Dosing errors of the study drug were noted in review. Subject # 96030/9018610 received full dose of CPT-11 (237mg) and 5-FU (948 mg) instead of reduced dose of CPT-11 (192 mg) and 5-FU (769 mg). When the dosage correction was calculated an incorrect reduced dose was given

Page 2 – Salim, M.D.

CPT-11 (144 mg) and 5-FU (576 mg) for 4 doses. Subject # 84792/9025429 received 5-FU (479 mg) instead of the correct dose of 5-FU (779 mg).

- 2) You did not report Adverse Events promptly to IRB as required. Gastrointestinal bleed was noted on subject 92501/9027466 physician's review notes. This adverse event was not reported to the sponsor. Subject 89397/9026406 had reported swelling in both feet to the nurse which was not reported to the sponsor.

In your discussion with the inspector, response to the Form FDA 483, you state that you will be more careful and thorough in completing documents in future studies you are involved with, and pay closer attention to administering study drugs, reporting adverse

We appreciate the cooperation shown Investigator Ballamy and Dr. Gan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Leslie Ball, M.D., Chief, Good Clinical Practice Branch II, by letter at the address given below.

Sincerely,

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

Page 3 – Salim, M.D.

CFN/FEI:

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI- no response required
- 3)VAI- response requested
- 4)OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:

- failure to obtain subject consent (0)
- failure to adhere to protocol (3)
- failure to notify IRB of AE (02)

cc:

HFA-224  
HFD-150 Doc.Rm. NDA# 21492  
HFD-150 Review Div.Dir. (Pazdur)  
HFD-150 MO ()  
HFD-150 PM ()  
HFD-46/47c/r/s/ GCP File #  
HFD-46/47 GCP Reviewer (Gan)  
HFR-CE700 DIB (Dempster)  
HFR-CE700 (Ballamy) Bimo Monitor  
HFR-CE700 Field Investigator (Ballamy)

Page 4 – Salim, M.D.

r/d: (REVIEWER):Gan:12/29/03  
reviewed:Ball:4/2/03

o:\Gan\SalimLR.doc

**Reviewer Note to Rev. Div. M.O.**

A total of 47 patients received the Investigational drug. 22 of the 47 were enrolled in the study period of 4/23/99 to 4/25/2001. These 22 patients included in the Type 6 NDA were inspected.

We reviewed the entire source documents and CRF for these 22 patients. Basically, the data from this site is OK. However, I would like to recommend to exclude 2 subjects, 92830 and 91091, from the final analyses. Subject #92830 did not meet the inclusion criteria in that he had uncontrolled hypertension and was enrolled in the study. Subject 91091 was not terminated from the study as required by protocol when he had progression of disease. A new lesion was detected by CT scans.

We also found some dosing errors and underreports of AEs. These errors might not have affected the end point of the study.

**Appears This Way  
On Original**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Robert J. Dalton, M.D.  
St. Mary's/Duluth Clinic Health System  
400 East Third Street  
Duluth, Minnesota 55805

Food and Drug Administration  
Rockville MD 20857

DEC 8 2003

Dear Dr. Dalton:

Between September 22 and 26, 2003, Ms. Sharon L. Matson, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # NCCTG N9741 entitled: "A Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL), 5-Fluorouracil (5-FU), and Irinotecan (CPT-11) as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum") of the investigational combinations of oxaliplatin, 5-Fluorouracil and Irinotecan, performed for Sanofi-Synthelabo. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

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

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

Sincerely,

  
Khin/Maung U, M.D.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

cc: Peter Person, M.D.  
CEO, St Mary's/Duluth Health System  
400 East Third Street  
Duluth, Minnesota 55805

FEI:

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD- Doc.Rm. NDA# 21-492/SE-002

HFD- Review Div.Dir. (Pazdur)

HFD- MO (Ibrahim)

HFD- PM (Cottrell)

HFD-46/47c/r/s/ GCP File # 9640

HFD-46 GCP Reviewer (Currier)

HFR-CE-850 DIB (Bigham)

HFR-CE850 Bimo Monitor (Matson)

GCF-1 Seth Ray

r/d:Currier: 11/03/03

reviewed:JPS:11/6/03

f/t:ml: 11/10/03

o:\cac\2003\daltonLTR.doc

**Reviewer Note to Rev. Div. M.O.**

This inspection was one of three issued to verify the data for NDA 21-492/SE-002. Dr. Dalton enrolled 45 subjects at 2 sites, Duluth and Thunder Bay. This inspection covered study records for 14 of the subjects at the Duluth site. There were no significant problems found with the conduct of the study. No 483 was issued to the investigator and the inspection is classified NAI.

Data from this study appear acceptable to use to support an approval decision for this supplement.

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

/s/

-----  
Khin U

12/8/03 11:36:50 AM

3 Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

     § 552(b)(4) Draft Labeling

## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Monday, January 05, 2004 1:45 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** RE: Response rate and TTP

Mark

My question was about these requirements not being prespecified in the original protocol as far as I could tell. Was there an addendum about these requirements?

Thanks

Amna

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

**From:** mark.moyer@us.sanofi.com [<mailto:mark.moyer@us.sanofi.com>]  
**Sent:** Monday, January 05, 2004 1:22 PM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** Re: Response rate and TTP

We received the following back from NCCTG regarding responders, which is in response to your question #3:

"A person was considered to be evaluable for response if they had at least 18 weeks of treatment (3 cycles on arm A, 9 cycles on arm F, or 6 cycles on arm G) or they went off treatment and had an end of active treatment form. If a patient had 2 consecutive responses (CR, PR, or regression) they were considered to have a confirmed response. There may have been cycles in between the responses where they weren't evaluated, which is fine. For example if they had a PR cycle 2, weren't evaluated cycle 3, and had a CR cycle 4 they were considered a confirmed response."

Regards,

Mark

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**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Friday, January 02, 2004 4:02 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** LIFE and EFC 7233

Mark,

Interim results of the above study are included in this NDA. Would it be OK with Sanofi if I put these results in my review? It can become public knowledge.

thanks,  
Amna

## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Wednesday, December 24, 2003 10:06 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** Response rate and TTP

Mark

I don't think we have the answer for #3. Please have it sent soon.

Please send the dataset used to create the exploratory analysis on TTP recently. My analysis finds FOLFOX to be better as well, but numbers are different. Who are the patients with measurable disease, progressors, there dates of progression etc.

Have a nice vacation.  
Amna

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

**From:** Ibrahim, Amna  
**Sent:** Tuesday, December 16, 2003 12:47 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** Response rate

Mark,

The number of patient evaluated for response is less than the ITT population.

- 1- Is it because this analysis was conducted for measurable disease patients only?
- 2- Was this specified in the protocol?
- 3- Was the 18 month on-treatment requirement and confirmation at 4 weeks also per protocol?

I have not found the 18 month requirement specified, and believe that the confirmation was supposed to be at 6 weeks. Please send me the reference for the area in protocol if and where these were specified.

thanks,  
Amna

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Tuesday, December 23, 2003 3:18 PM  
**To:** 'mark.moyer@us.sanofi.com'; Ibrahim, Amna  
**Cc:** Cottrell, Christy; Johnson, John R  
**Subject:** RE: TTP analysis

Thanks Mark

Do your statistician have a SAS dataset they created for this analysis. If so, please send it/them to me.

Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Tuesday, December 23, 2003 3:10 PM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy; Johnson, John R  
**Subject:** Re: TTP analysis

In response to your request for the TTP based on patients with measurable disease and based on the criteria outlined in your Email, Sanofi-Synthelabo has prepared the attached Word document.

(See attached file: Time to Progressionmeasurable.doc)

Kindest Regards,

Mark

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## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Tuesday, December 23, 2003 2:42 PM  
**To:** Cottrell, Christy; 'mark.moyer@us.sanofi.com'  
**Subject:** RE: Financial Disclosure

Mark  
Please submit the name of this investigator. We understand that the amount was not contingent on the results of the study.  
Thanks  
Amna

-----Original Message-----  
**From:** Cottrell, Christy  
**Sent:** Tuesday, December 23, 2003 2:24 PM  
**To:** Ibrahim, Amna  
**Subject:** FW: Financial Disclosure

Amna,  
  
Can you answer Mark's question re: financial disclosure?

Christy  
  
-----Original Message-----  
**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Tuesday, December 23, 2003 2:20 PM  
**To:** Cottrell, Christy  
**Subject:** RE: Financial Disclosure

Christy,  
  
We completed the review of our finance department records for all of the investigators that participated in — Out of the 316 investigators that participated, only 11 were paid as consultants. Of these 11, only — had fees during the conduct of the study from Jan 1998 to Dec. 2002 totaling in excess of the \$50,000 limit, and this investigator only entered —  
Therefore, I am able to complete a revised Form FDA 3454 with the 2nd category checked. My question is what needs to be included regarding this [ ] Do I need to include [ ] name and the amounts paid and when? None of these funds were contingent on the results and reflect general consulting services, including honoraria for speaking engagements.

Regards,  
  
Mark

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**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Friday, December 19, 2003 12:58 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Johnson, John R  
**Subject:** TTP analysis

Hi Mark

Please have the following new analysis performed on TTP of patients with measurable disease as soon as possible and send it to us.

Suggestions:

- 1- Subset measurable disease patients (if there is at least one lesion at baseline (earliest cycle), I am counting that patient as a measurable disease patients).
- 2- rows where number of lesions is less than baseline should be excluded from analysis.
- 3- TTP progression based only on measurable disease (without new lesions or accounting for evaluable lesions) should be calculated. Patient who do not progress are censored.

thanks,  
Amna

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Wednesday, December 17, 2003 12:58 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** Study period

Hi Mark,

In the figure on Study time lines as well as the summary of amendments, the study report states that the 795 patients were randomized starting April 23, 1999.

Page 29 section 8, last para states that "This study report summarizes the efficacy and safety results for the population of 795 patients randomized to Arms A, F, and G from 20 May 1999 to 25 April 2001."

Can you tell me which one is correct?

thanks,  
Amna

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Tuesday, December 16, 2003 12:47 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** Response rate

Mark,

The number of patient evaluated for response is less than the ITT population.

- 1- Is it because this analysis was conducted for measurable disease patients only?
- 2- Was this specified in the protocol?
- 3- Was the 18 month on-treatment requirement and confirmation at 4 weeks also per protocol?

I have not found the 18 month requirement specified, and believe that the confirmation was supposed to be at 6 weeks. Please send me the reference for the area in protocol if and where these were specified.

thanks,  
Amna

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Friday, December 12, 2003 9:28 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** RE: PT, PTT and anticoagulation

Mark  
The table is very helpful. However, as I go through the table, I have certain questions. Please send me the CRFs for the 13 patients with PT or PTT related AEs electronically. Please do let me know how soon you can send me these for obvious reasons. Thanks Amna

-----Original Message-----  
From: mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
Sent: Thursday, December 11, 2003 3:59 PM  
To: Ibrahim, Amna  
Cc: Cottrell, Christy  
Subject: Re: PT, PTT and anticoagulation

Attached as a Word document is a table with all the subjects identified with PT or PTT. The table includes, "Sponsors Review of CRF's", which is information that was obtained from review of the case report forms.

Regards,

Mark

(See attached file: PT&PTTREVIEW.doc)

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## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Friday, December 12, 2003 8:33 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** RE: crossover

Mark  
Why is there a difference between Sanofi's numbers and those in the NCCTG paper in the JCO for people crossing over?  
Amna

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

From: mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
Sent: Thursday, December 11, 2003 4:25 PM  
To: Ibrahim, Amna  
Cc: Cottrell, Christy  
Subject: Re: crossover

The following is more detailed information on how to approach the dataset to identify crossover.

On the Event Monitoring Form (data table = EVENT) there is a question asking about treatment following disease progression.

(Embedded image moved to file: pic30093.pcx)

We counted a patient as receiving post-study cpt-11 if there was any record in the EVENT table with

CT\_REC\_F = 'Yes' and FU\_DATE not missing  
and CPT11U\_F = 'Yes'

(FU\_DATE is the date of the last contact or death, recorded at the top of the Event Monitoring Form)

Likewise for oxaliplatin: CT\_REC\_F = 'Yes' and FU\_DATE not missing  
and OXAL\_U\_F = 'Yes'

For 5-FU: CT\_REC\_F = 'Yes' and FU\_DATE not missing  
missing and FVFU\_U\_F = 'Yes'

For other: CT\_REC\_F = 'Yes' and FU\_DATE not missing  
and OTHER\_F = 'Yes'

-----  
This logic produced the following table in the study report. Note that it is restricted to patients who were treated (SF\_ARM = 'A', 'F', or 'G').

(Embedded image moved to file: pic16565.pcx)

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## Cottrell, Christy

---

**From:** Cottrell, Christy  
**Sent:** Thursday, December 11, 2003 4:20 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Subject:** Clarification on requests from Dr. Rothmann

Mark,

Dr. Rothmann just spoke with me and wanted to make a clarification on his request for the updated survival analysis. He said that the updated survival analysis that you submitted was the same as was already submitted and included data through the July 1998 cut-off. During the March 2000 ODAC (page 91 of the transcripts), during a conversation with Dr. Simon, you mentioned having updated survival analysis data through a cut-off of December 1998. This was the information that Dr. Rothmann was interested in. If you are able to provide this information by very early next week (Monday or Tuesday), we would like you to submit it. Otherwise, if you can't pull the info together that quickly, we won't have time to review it for this action since we're nearing the end of the review time.

Also, Dr. Rothmann pointed out an inconsistency that he found in your ITT survival analysis for study 7233. In the table, N for FUFOX is 123 and N for Mayo is 129. These numbers are correct, however, the % censored for these groups don't match (25.8% and 22.0%, respectively).

Thanks,  
Christy

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Friday, December 05, 2003 8:19 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** JCO article

Hi Mark

If it is problematic to get the JCO article, it would be ok to send us whatever study report that NCCTG may have given to Sanofi.

thanks,  
Amna

## Cottrell, Christy

---

**From:** Cottrell, Christy  
**Sent:** Thursday, December 04, 2003 3:50 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Subject:** Re: requests from Dr. Rothmann

Mark-

See below for our responses:

Based on your Email, I interpret this to mean you still have access to the EFC2961 dataset and the old EFC2962 dataset. Therefore, all we need to submit is the updated dataset for survival for EFC2962, which I will be sending today.

- Yes, that is fine.

By the way, we are not familiar with the names of the datasets you noted. Are these FDA assigned names? We do not have a Cox dataset for these two studies.

- These were not FDA assigned names. Files were located at the path that sent to Sanofi-Synthelabo. There were four SAS transport files at that location with created/saved dates and times of 7/9/1999 1:08 pm, 7/9/1999 1:12 pm, 7/3/1999 3:22 pm, and 7/3/1999 3:22 pm (two of the files having the same created/saved times of 3:22).

Hope this helps,  
Christy

## Cottrell, Christy

---

**From:** Cottrell, Christy  
**ent:** Thursday, December 04, 2003 2:55 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Ibrahim, Amna  
**Subject:** Status of Sanofi responses to inquiries

Mark,

In order to help you prioritize, these are the four items that we need most urgently at this point:

1. As you noted in your 12-2-03 e-mail, the marked-up copy of the labeling you sent is "redundant" because there are sections that were moved, but are shown as strikethrough and then later in the document as additions. We would like a "less redundant" marked-up version of the labeling as soon as possible.
2. The JCO article that Amna requested on 12-1-03.
3. A response to Amna's request earlier today for the number of patients with increased PT, PTT reported as AEs who were on anticoagulation.
4. A response to Amna's request of 11-28-03 for the following:

1-Several patients in the study had pneumonitis. One patient 7462 2314 092960 on SF\_ARM A had oxaliplatin listed as a possible cause in the dataset. No cycle # is listed. Did this happen after patient crossed over to oxaliplatin?  
2-When patients were crossed over after progression, did they continue to be reported in the original SF\_ARM?

Although not quite as urgent, we are also awaiting your response to Amna's 11-26-03 request for the percentage of patients that SWOG audited internally.

Thanks,  
Christy

**Cottrell, Christy**

---

**From:** Ibrahim, Amna  
**Sent:** Thursday, December 04, 2003 8:58 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** PT, PTT and anticoagulation

Mark  
The have been incidences of increased PT, PTT reported as AE. How many of these patients were on anticoagulation?

thanks,  
Amna

**Cottrell, Christy**

---

**From:** Cottrell, Christy  
**Sent:** Wednesday, December 03, 2003 1:33 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Subject:** RE: Requests from Dr. Rothmann

Mark,

See the attached response from Dr. Rothmann:

For study EFC2962, updated data on survival only is acceptable.

We will be analyzing data for this review from datasets (e.g., Cox\_2961 and Cox\_2962) that were submitted by Sanofi-Synthelabo in July/August 1999 (dated July 22, 1999) for the review of NDA 21063 (N000). The datasets Cox\_2961 and Cox\_2962 were located at crt\datasets\ise. If Sanofi-Synthelabo would like to receive copies of these datasets, we are willing to provide you with copies.

Christy

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Tuesday, December 02, 2003 2:11 PM  
**To:** Cottrell, Christy  
**Subject:** Re: Requests from Dr. Rothmann

Christy,

We should have the information on the EFC7233 by Thursday of this week. This study was not conducted by the Sanofi-Synthelabo Research Group, so we have to go back to the sponsoring group to get these results, since we do not have the database.

Regarding the datasets, we have the updated EFC2962 dataset that was presented at ODAC. However, the dataset we have for EFC2961 is the same as the one submitted in the NDA. Please check with Dr. Rothman to make sure that this is okay. The publication for EFC2961 has an updated survival analysis (131 events), which we do not have the database. Also, we plan to submit just the databases for the survival analysis and not all of the others for these studies. Please confirm that these are all FDA needs. I will then be able to sent the databases via Email and then formally submit via CD-ROM and a submission.

Regards,

Mark

Moyer/US-PA-GV/RESEARCH/SANOFI@Research  
Rothmann

"Cottrell,  
Christy"  
<CottrellC@cdcr.  
fda.gov>

To: Mark  
cc:  
Subject: Requests from Dr.

11/26/2003 10:35  
AM

Mark,

I received your voicemail yesterday, and we looked into the old minutes.....see the response below from Dr. Rothmann:

The first item comes from the Pre-sNDA content meeting of May 7, 2003. This information is needed to determine the reliability of any TTP analysis. The p-value is used to state the strength of evidence against a specific hypothesis (that the two arms have the same theoretical TTP distribution). The p-value does not, for example, provide any information on how accurate is the measured difference between the distributions. The minimal amount of additional information needed from the sponsor to determine this would be the number of events in each arm for the data that was used in the TTP analysis.

For item 2, we could not find anything in any written meeting minutes about providing the data for the updated analysis for study EFC2962 that you presented at ODAC, although Dr. Rothmann recalls requesting this verbally during one of the meetings. You presented the updated survival analysis at ODAC which gave a slightly better comparison for FOLFOX-4 than the earleir analysis. It would be nice to have the most updated data, but it is not necessary.

Also, on a separate note, we're still waiting for the marked up version of the labeling for S-002 (see my e-mail request dated November 19th). We have some internal meetings scheduled for next week and labeling may come up. We need to be able to know what was added/changed with this supplement.

Thanks!  
Christy

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## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Friday, November 28, 2003 11:32 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Pneumonitis & crossover

Mark

1-Several patients in the study had pneumonitis. One patient 7462 2314 092960 on SF\_ARM A had oxaliplatin listed as a possible cause in the dataset. No cycle # is listed. Did this happen after patient crossed over to oxaliplatin?

2-When patients were crossed over after progression, did they continue to be reported in the original SF\_ARM?

Regards  
Amna

## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Wednesday, November 26, 2003 8:12 AM  
**To:** 'mark.moyer@us.sanofi.com'; Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** RE: Missing Inclusion/Exclusion data

Mark:  
Has SWOG told you what percentage of patients they audited internally, yet?  
Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Tuesday, November 25, 2003 8:51 AM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** RE: Missing Inclusion/Exclusion data

We were aware that there was a meeting with NCCTG, since Rick Pazdur contacted me to ask permission to speak with them regarding database issues and conventions. We checked again with NCCTG regarding these 116 SWOG patients, and they informed us that the SWOG patient eligibility was checked within SWOG and not NCCTG for these 116 patients. The only thing that NCCTG received was whether or not the patient was eligible, yes or no. There was no electronic system at that time for the investigators to randomize the patients, in which they had to respond to questions of eligibility prior to randomization.

If you need further clarification, please let me know.

Regards,

Mark

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## Cottrell, Christy

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**From:** Ibrahim, Amna  
**Sent:** Monday, November 24, 2003 12:33 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Median # of cycles on FOLFOX

Hi Mark

According to the study report, the median # of cycles on the FOLFOX arm is 10. According to my analysis, the median # is 7. I counted only those cycle where oxaliplatin was administered. Was there a difference in methodology of the analysis leading to the difference?

Regards  
Amna

## Cottrell, Christy

**From:** Rothmann, Mark D  
**Sent:** Thursday, November 20, 2003 2:36 PM  
**To:** Cottrell, Christy  
**Cc:** Ibrahim, Amna  
**Subject:** RE: Prog time zero

Reply to Mark Moyer:

In the dataset CRSE, there ARE twelve patients (listed below) who were listed as having progressed (as having an event) at time zero. This is the dataset for which the submitted primary analysis on TTP was based. The submitted primary analysis on TTP was not based on a dataset that had twelve patients in the IFL arm that were listed as having an event for TTP at time zero.

Row	ARM_FMT	CLIN_ID	PG_STAT	PG_STA_F	PG_TIME
1	IROX	7462 0504 081065	2	PROGRESSION	0
2	IROX	7462 0163 084040	2	PROGRESSION	0
3	IROX	7462 1742 084944	2	PROGRESSION	0
4	FOLFOX4	7462 1798 089253	2	PROGRESSION	0
5	IROX	7462 1796 089823	2	PROGRESSION	0
6	IFL	7462 1249 090291	2	PROGRESSION	0
7	IROX	7462 2338 090748	2	PROGRESSION	0
8	IROX	7462 2343 091274	2	PROGRESSION	0
9	IFL	7462 0497 091305	2	PROGRESSION	0
10	IROX	7462 0282 091923	2	PROGRESSION	0
11	IROX	7462 2290 092242	2	PROGRESSION	0
12	FOLFOX4	7462 1822 093298	2	PROGRESSION	0

In addition twenty-one patients (17 in the IFL arm, 2 in the FOLFOX-4 arm and 2 in the IROX arm) had their TTP censored at time zero. These patients are listed below.

Row	ARM_FMT	CLIN_ID	PG_STAT	PG_STA_F	PG_TIME
1	IFL	7462 2262 087052	1	NO PROGRESSION	0
2	FOLFOX4	7462 1742 089582	1	NO PROGRESSION	0
3	IFL	7462 0438 089972	1	NO PROGRESSION	0
4	IFL	7462 0438 091435	1	NO PROGRESSION	0
5	IFL	7462 1062 091486	1	NO PROGRESSION	0
6	FOLFOX4	7462 0720 091555	1	NO PROGRESSION	0
7	IFL	7462 1242 091760	1	NO PROGRESSION	0
8	IFL	7462 0438 092093	1	NO PROGRESSION	0
9	IFL	7462 0643 092289	1	NO PROGRESSION	0
10	IFL	7462 1038 092494	1	NO PROGRESSION	0
11	IFL	7462 0363 092595	1	NO PROGRESSION	0
12	IFL	7462 1571 093081	1	NO PROGRESSION	0
13	IFL	7462 0558 093411	1	NO PROGRESSION	0
14	IFL	7462 2243 093480	1	NO PROGRESSION	0
15	IFL	7462 0385 093724	1	NO PROGRESSION	0
16	IROX	7462 1143 093828	1	NO PROGRESSION	0
17	IFL	7462 2161 093838	1	NO PROGRESSION	0
18	IFL	7462 1038 093867	1	NO PROGRESSION	0
19	IROX	7462 2095 094348	1	NO PROGRESSION	0
20	IFL	7462 1249 094607	1	NO PROGRESSION	0
21	IFL	7462 1742 094793	1	NO PROGRESSION	0

-----Original Message-----  
From: Cottrell, Christy

Sent: Thursday, November 20, 2003 2:03 PM  
To: Rothmann, Mark D  
Cc: Ibrahim, Amna  
Subject: FW: Prog time zero

Mark,

See below. Which patients are you referring to?

Christy

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

From: mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
Sent: Thursday, November 20, 2003 1:51 PM  
To: Cottrell, Christy  
Cc: Ibrahim, Amna  
Subject: RE: Prog time zero

As an initial response to your fax dated 11/19/03 requesting information on "12" patients with progression event at time zero, there were actually 22 patients.

12 on Arm A, 2 on Arm F and 8 on arm G.

Can FDA provide a listing of the 12 patients in question ?

Regards,

Mark

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**Cottrell, Christy**

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**From:** Ibrahim, Amna  
**Sent:** Thursday, November 20, 2003 12:40 PM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Patients in efficacy datasets

Mark  
Were any patients excluded from the efficacy analysis?  
Thanks  
Amna

## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Tuesday, November 18, 2003 10:43 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Safety population and ineligibility

Hi Mark

According to dataset CYTOX, "EXCUD\_F" has 3 patients as ineligible and 2 as having major violations.

They are:

7462 0120 084723	Ineligible	G
7462 0254 095060	Ineligible	G
7462 0370 090972	Major Violation	F
7462 0534 091873	Major Violation	G
7462 1621 092140	Ineligible	F

Can you give me the details for ineligibility for the three? You have given me the reasons for protocol violation. Were any the above 5 patients excluded from your safety evaluation? They were in the EXCLUDED column in an AE dataset.

Thanks  
Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Monday, November 17, 2003 4:53 PM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** RE: Safety population

I forgot to respond to your question regarding the protocol violations, which are as follows:

Pt 9026902 {subjid = 90972} was assigned to Arm F; pt was supposed to receive 2 days of 5FU infusion but only received 5FU infusion for the first day only of each cycle.

Pt 9027035 {subjid = 91357} was declared ineligible because he had received standard adjuvant rectal cancer chemoradiation prior to study entry; this was a contraindication to eligibility.

Pt 9027214 {subjid 91873} was assigned to receive Arm G, but the pt was given Arm A.

**Cottrell, Christy**

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**From:** Ibrahim, Amna  
**Sent:** Thursday, November 20, 2003 10:37 AM  
**To:** 'mark.moyer@us.sanofi.com'; Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** RE: Safety population and ineligibility

Mark  
Can you give me the CLIN\_ID for the patients mentioned below.  
Thanks  
Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Thursday, November 20, 2003 10:09 AM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** Re: Safety population and ineligibility

We did not exclude any patients for ineligibility or protocol violations. I am preparing a separate Email regarding further clarifications for the safety analysis.

In response to the ineligible patients, the NCCTG provided the following:

Pt 9025417 - pt received prior RT to >15% of bone marrow prior to on study; contra to eligibility. Pt 9028260 - pt had surgery following on study; pathology indicated that the actual primary was pancreas and not a colon primary. Pt 9027316 - pt had diabetic neuropathy at baseline, also PS was determined to be a 3 vs 2 or less at baseline, both of these were contras to the study eligibility requirements. These were audit findings.

Regards,

Mark

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## Cottrell, Christy

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**From:** Ibrahim, Amna  
**Sent:** Thursday, November 13, 2003 9:35 AM  
**To:** Ibrahim, Amna; 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy  
**Subject:** RE: Safety population

Actually when I combine CYTOXNCI and CYTOX as was done for the study report, there are only 766 patients in these datasets. Please tell me who and why were some patients excluded from this dataset.  
Thanks  
Amna

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

**From:** Ibrahim, Amna  
**Sent:** Friday, November 07, 2003 10:12 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Safety population

Mark

There are apparently 3 datasets for safety. They have a maximum 769 patient in these datasets, whereas there were 773 patients in the safety population. Is that because 4 patients did not have any AEs?

2 patients had major violations. What were they?

thanks,  
Amna

## Cottrell, Christy

---

**From:** Ibrahim, Amna  
**Sent:** Friday, November 07, 2003 4:00 PM  
**To:** 'mark.moyer@us.sanofi.com'; Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** RE: Last contact date

Mark  
The IDs are as follows:

7462 0008 079908  
7462 0008 090075  
7462 0153 093391  
7462 0163 089499  
7462 0169 080805  
7462 0197 090166  
7462 0370 090972  
7462 0522 090655  
7462 0522 090882  
7462 0675 093583  
7462 0960 090066  
7462 1021 084910  
7462 1027 084639  
7462 1027 091037  
7462 1038 086572  
7462 1038 089682  
7462 1184 090718  
7462 1207 091357  
7462 1251 092205  
7462 1278 086237  
7462 1278 094269  
7462 1680 090982  
7462 2213 095357  
7462 2301 089595  
7462 2311 090647  
7462 2333 090588  
7462 2380 092153

Thanks  
Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Friday, November 07, 2003 3:51 PM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** Re: Last contact date

In order to make sure that we address your question fully can you send us a list of the patients. We think we have an answer, but this would help us verify our response.

Thank you,

Mark

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## Cottrell, Christy

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**From:** Ibrahim, Amna  
**Sent:** Friday, November 07, 2003 10:12 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** Safety population

Mark

There are apparently 3 datasets for safety. They have a maximum 769 patient in these datasets, whereas there were 773 patients in the safety population. Is that because 4 patients did not have any AEs?

2 patients had major violations. What were they?

thanks,  
Amna

## Cottrell, Christy

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**From:** Ibrahim, Amna  
**Sent:** Friday, November 07, 2003 10:11 AM  
**To:** 'mark.moyer@us.sanofi.com'  
**Cc:** Cottrell, Christy; Ibrahim, Amna  
**Subject:** RE: Missing Inclusion/Exclusion data

Mark...  
As you probably know, some of the NCCTG members were at the FDA yesterday for an unrelated meeting. They said that they have an electronic process for randomization in place. At the time of randomization, there are required fields for entry criteria that must be filled before the patient can be entered in to the study. Was this procedure in place at the time this study was conducted? Did the SWOG patients also get enrolled by this mechanism?

Thanks  
Amna

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

**From:** mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
**Sent:** Thursday, November 06, 2003 4:35 PM  
**To:** Ibrahim, Amna  
**Cc:** Cottrell, Christy  
**Subject:** RE: Missing Inclusion/Exclusion data

In response to your Email attached below, besides the 116 SWOG patients who did not have inclusion/exclusion data at all, there are 100 patients missing some data. The number of patients with some/all missing inclusion/exclusion data are summarized in a table in the Word document that is attached.

As you will see in the attachment, most of the missing data (besides the 116 SWOG patients) occurred in inclu0021 and exclu19.

For item inclu021, only center that participated in the quality of life questionnaire were required to fill out this item. Those that did not complete this information did not participate in this portion of the study.

For item exclu019, this item was added to the CRF starting on 10/19/01. Therefore, all 796 patients in our submission should not have data on this item. We found 13 patients had data "No" for this item. These patients were enrolled very early from May 1999 to June 1999. Therefore, this item would not be completed for these patients. These patients are as follows:

SUBJID	NCCTG_ID	ARM
78841	9024494	G
78845	9024497	F
78859	9024499	A
78902	9024519	G
79009	9024554	F
79078	9024580	F
79178	9024615	G
79237	9024635	A
79380	9024655	F
79424	9024664	G
79425	9024665	A
79467	9024681	G

(See attached file: Number of patients with missing inclusion.doc)

"Ibrahim, Amna"

<IbrahimA@cder.fda.gov>  
Moyer/US-PA-GV/RESEARCH/SANOFI@Research  
Christy" <CottrellC@cder.fda.gov>  
<IbrahimA@cder.fda.gov>  
10/28/2003 04:15  
Inclusion/Exclusion data  
PM

To: Mark  
cc: "Cottrell,  
"Ibrahim, Amna"  
Subject: RE: Missing

Mark

There were an additional 100 patients who had some missing values for inclusion criteria. I have attached the patient IDs that I have found for these patients. Do you know why this list of patient did not have complete datasets for inclusion criteria?

<<missing values.doc>>

Thanks  
Amna

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

From: Ibrahim, Amna  
Sent: Tuesday, October 28, 2003 3:39 PM  
To: 'mark.moyer@us.sanofi.com'  
Cc: Cottrell, Christy  
Subject: RE: Missing Inclusion/Exclusion data

Mark

Thanks for your response. Who performed the audits you mentioned below and how were they performed? Were all CRFs looked at for inclusion and exclusion criteria?

Any idea when the patient profiles might be ready?  
Regards,  
Amna

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

From: mark.moyer@us.sanofi.com [mailto:mark.moyer@us.sanofi.com]  
Sent: Tuesday, October 28, 2003 3:35 PM  
To: Ibrahim, Amna  
Cc: Cottrell, Christy  
Subject: RE: Missing Inclusion/Exclusion data

Amna,

We followed up with NCCTG regarding the 116 patients missing the

inclusion/exclusion criteria data, and they looked into this and contacted SWOG, which provided the following:

"I checked w/Random Office on this one. All of the pts listed below are SWOG memberships. Approximately 10 yrs ago, the SWOG central office declared they would no longer be completing Eligibility Checklists except for the Strat Factor section. This was due to cutbacks and it applies to all protocols that SWOG participates in. Any errors would be found during the audit process. This arrangement was approved by our administrator Sharon Elcombe"

Please let me know if this addresses your question, and if we need to do anything further.

Regards,

Mark Moyer

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(See attached file: missing values.doc)

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