DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-492/S-002

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 supplemental new drug application dated July 11, 2003, received July 11, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELOXATIN® (oxaliplatin) for Injection.

We acknowledge receipt of your submissions dated August 12, September 4 and 11, October 22, 28, 30, and 31, November 7, 11, 12, and 21, and December 2, 4, 15 (2), and 16 (2), 2003.

This supplemental new drug application provides for the use of ELOXATIN® in combination with infusional 5-Fluorouracil (5-FU) and Leucovorin (LV) for the treatment of patients previously untreated for advanced colorectal cancer.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-492/S-002." Approval of this submission by FDA is not required before the labeling is used.

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your Commitment #3 made under 21 CFR 314.510 as described below.

> Complete study EFC7462 (Randomized, Phase 3 trial of Combinations of Oxaliplatin, 5-Fluorouracil and Irinotecan as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum). Submit the full study report for review by 2003, third quarter.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

The postmarketing study commitments listed below were part of the original commitments in our approval letter dated August 9, 2002. However, because clinical benefit has been demonstrated in Study EFC7462, we are hereby releasing you from the selected postmarketing commitments listed below.

1. Complete the study whose initial results were submitted for review in NDA 21-492: EFC4584 (Multi-center, Randomized, Three Arm Study of 5-Fluorouracil/Leucovorin or Oxaliplatin or a Combination of 5-Fluorouracil and Oxaliplatin as Second-Line Treatment of Metastatic Colorectal Carcinoma). Submit the mature survival data and analysis in a final study report for review by 2004, second quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by second quarter, 2004

2. Complete study EFC4585 (Multi-center, Randomized, Two Arm Study of Irinotecan versus the Combination of Oxaliplatin with Irinotecan as Second Line Treatment of Metastatic Colorectal Cancer). Submit the mature survival data in a full study report for review by 2005, third quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by third quarter, 2005

4. Complete study L8125 (Randomized Trial Evaluating Oxaliplatin Combined with Two Different 5-Fluorouracil Regimens in Patients with Previously Untreated Advanced Colorectal Cancer). Submit the full study report for review by 2005, second quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by second quarter, 2005

5. Complete the adjuvant treatment study EFC3313 (Multicenter International Study of Oxaliplatin/5FU/LV in the Adjuvant Treatment of Colon Cancer - MOSAIC TRIAL). Submit the full study report for review by 2004, third quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by third quarter, 2004

6. Complete the adjuvant treatment study EFC7112 (Clinical Trial Comparing 5-FU plus Leucovorin and Oxaliplatin with 5-FU/LV for the Treatment of Patients with Stage 2 and 3 Carcinoma of the Colon). Submit the full study report for review by 2007, first quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by first quarter, 2007

10. Complete the study EFC4759 (Single Arm Phase 2 study of Oxaliplatin as Third-Line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, third quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by third quarter, 2004

11. Complete the study EFC 4760 (Randomized, Phase 2 Trial of Infusional 5-FU versus Infusional 5FU/Oxaliplatin in 3rd line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, first quarter.

Protocol Submission:	Completed
Study Start:	Completed
Final Report Submission:	by second quarter, 2004

We remind you of your pending postmarketing study commitments in our approval letter dated August 9, 2002. These commitments are listed below.

7. Design and conduct a study to examine the safety of administering repeated doses of oxaliplatin 85 mg/m squared in combination with infusional 5-FU/LV, at the doses and schedule recommended in the product label, in patients with varying degrees of renal impairment. This study should include patients with normal renal function, minimally impaired renal function, and moderately impaired renal function. The study should be designed to assess whether there are differences in safety between each of the different subgroups of renal impairment and a control group with normal renal function. Differences in proportions of patients with all grades and grade 3/4 gastrointestinal, neurological, renal and hematological toxicities, differences in time to onset and duration of grade 3/4 neurotoxicity, and differences in proportions of patients who require dose reductions should be evaluated. A subgroup of patients with severe renal toxicity should also be considered for study, possibly at a lower starting dose. Submit the full study report for review by 2004, third quarter.

Protocol Submission:	Completed
Study Start:	by first quarter, 2004
Final Report Submission:	by third quarter, 2004

8. Submit reports of all medication errors, both potential and actual, that occur within the United States with oxaliplatin for two years following the date of approval. Potential errors should be reported and summarized quarterly. All actual errors should be submitted within 15 days regardless of patient outcome. Yearly reports of potential and actual errors occurring with oxaliplatin should be submitted for two years following the date of approval.

Protocol Submission:	N/A
Study Start:	August 9, 2002
Final Report Submission:	August 9, 2004

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure

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

/s/

Richard Pazdur

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