DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-492

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

Attention: Mark Moyer
Vice President, Drug Regulatory Affairs

Dear Mr. Moyer:

Reference is made to your Proposed Pediatric Study Request submitted on July 29, 2004, for ELOXATIN™ (oxaliplatin) Injection to IND (b) (4)

To obtain needed pediatric information on oxaliplatin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients described below. These studies investigate the potential use of oxaliplatin in the treatment of children with cancer.

Background:

The development of pediatric oncology drugs presents certain difficulties but is also facilitated by current practices. Compared to most adult malignancies, pediatric cancers afflict small numbers of patients, making formal outcome studies difficult. On the other hand, because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved therapies and effective treatment for patients refractory to current therapy. Early access to new drugs is one mechanism to achieve this goal.

Although in some cases pediatric claims for treatment of a malignancy can be based on results in adults, with appropriate PK and safety information in the pediatric population, the many known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. It is usually necessary to evaluate the effectiveness and safety of new drugs in pediatric populations. In the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA would ordinarily expect to rely on demonstration of tumor response as the basis of approval; other endpoints would probably be used in disease stages where there is existing therapy. In refractory settings, and with rare disease, it may be appropriate to rely on relatively small amounts of safety data.

- *Type of studies needed*:

  Phase 1 studies: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered must be sufficient to achieve Phase 1 objectives; this would require 18-25 patients. Two Phase 1 studies are to be submitted.

  Phase 2 or pilot studies: These studies must enroll at least 14 pediatric patients with refractory or relapsed tumors per trial and must obtain pharmacokinetic data. Studies must be performed at facilities that have the experience, support, and expertise to care for children with cancer. Two Phase 2 studies are to be submitted.

- *Indication(s) to be studied (i.e., objective of each study):*

  Refractory or relapsed pediatric solid tumors

- *Age group in which study(ies) will be performed*:

  Infants > 1 month of age to adolescents up to 21 years of age with a distribution of patients that reflects the demographics of the diseases under study

- *Study endpoints:*

  The Phase 1 studies should seek the maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, and pharmacokinetic (PK) parameters including clearance, volume of distribution and half-life as secondary endpoints. A traditional or sparse sampling technique should be used to estimate the pharmacokinetic parameters.

  The Phase 2 or pilot studies must have a disease-specific surrogate endpoint or a clinically relevant endpoint. A traditional or sparse sampling technique should be used to estimate the pharmacokinetic parameters.

  Data from the Phase 1 and Phase 2 studies should be combined to develop population pharmacokinetic and pharmacodynamic (PK-PD) models and to explore PK-PD relationships for measures of safety and effectiveness.

- *Drug information submitted:*
  - *route of administration:* Intravenous
  - *regimen:* As determined by Phase 1 study. If you are using doses in Phase 2 studies that have not been justified by the Phase 1 studies, you must provide adequate justification for using such doses.

- *Drug specific safety concerns*:

  Peripheral neuropathy, neutropenia, thrombocytopenia, bleeding, infections, anemia, hepatotoxicity and death

- *Statistical information, including power of study and statistical assessments:*

  Statistical analysis appropriate to the phase of the study, including descriptive statistics for the Phase 2 studies must be submitted. Descriptive statistics for the PK parameters, clearance, half-life, volume of distribution and area under the curve must be included.

- *Labeling that may result from the studies*:
  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*:
  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

- *Timeframe for submitting reports of the studies:*
  Reports of the above studies must be submitted to the Agency on or before August 8, 2006. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

- *Response to Written Request:*

  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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

Sincerely,

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

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

/s/

Robert Temple

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