DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT # 1

NDA 20-896

Hoffmann-La Roche, Inc.
Attention: Antonella Lozito, Pharm. D, R.Ph.
Program Manager, Oncology
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Lozito:

Reference is made to your Proposed Pediatric Study Request submitted on November 1, 2004 for Xeloda® (capecitabine, Ro 09-1978) to IND 45,305.

Please also refer to your submissions dated September 16 and December 5, 2005.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated March 16, 2005.

Background:

The design of studies in pediatric oncologic drug development is discussed in detail in the guidance for industry, *Pediatric Oncology Studies in Response to a Written Request* at http://www.fda.gov/cder/guidance/3756dft.htm. Please refer to this guidance for additional information.

Protocols for each of your studies should be submitted to the FDA for review prior to initiation of the studies. Each submission should review the overall development plan and justify the study design(s).

- **Types of studies:**

  Open-label, non-randomized, phase 1 - 2 dose finding, pharmacokinetic (PK), safety, and efficacy study of capecitabine in combination with radiation in patients with primary brain stem tumors.

- **Indication to be studied**:

  Children with newly-diagnosed non-disseminated intrinsic diffuse brain stem gliomas.

- **Age groups in which studies will be performed:**

1. In the Phase 1 portion of the study, the PK substudy will include approximately 9 patients in each of the following two age groups: age 2 months to 6 years and 7 years to 12 years. When the MTD has been reached or exceeded, an additional 3 or more patients will be treated at a dose level selected to provide further evidence of safety and anti-tumor activity.

2. In the phase 2 portion, a minimum of 40 patients under age 18 will be enrolled, unless adverse findings require early stopping. Consideration for early stopping must include discussion with FDA. The study protocol for the phase 2 study portion, addressing the issues outlined in this request, are to be submitted to the Agency for review and agreement prior to study initiation. Do not commence any study before FDA review of the protocol.

- **Study endpoints:**

1. The primary purpose of the phase 1 portion of the study will be to determine the maximal tolerated dose (MTD) and dose-limiting toxicities (DLT) of capecitabine when administered concurrently with radiation therapy. Secondary objectives will include a description of the safety profile of the capecitabine-radiation therapy combination and an evaluation of the pharmacokinetics of capecitabine and its metabolites in pediatric age patients. Additionally, pharmacokinetic and pharmacodynamic (PK-PD) models will explore exposure-response relationships for measures of safety and effectiveness.

2. In the phase 2 portion of the study, the primary endpoint shall be progression-free-survival. Secondary endpoints will include response rate, overall survival, and one year survival. A comparative assessment with contemporary cooperative group historical controls will be performed. In addition, the study should provide an assessment of the safety of the addition of Xeloda® to brain radiation in this setting.

- **Drug information:**

  - *Dosage form:* Rapid-disintegrating flavored tablet.

  - *Route of administration*: Oral

  - *Regimen:* Oral capecitabine will be administered daily in two divided doses approximately 12 hours apart beginning within 24 hours of the start of radiation therapy and may continue for 4 weeks post completion of the radiation.

  - *Formulation:* Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents: detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- **Drug specific safety concerns:**

1. The safety and efficacy of capecitabine combined with radiation has not been evaluated in children with brainstem gliomas. Radiation therapy should be given in a typical manner, using conventional or conformal volume-based techniques at standard doses.
2. Safety evaluations must include clinical and neurologic examinations, evaluation of adverse events, and laboratory studies including CBCs, electrolytes, assessments of renal and hepatic function, and assessment of potential drug interactions with dexamethasone and anti-seizure medications, if these medications are co-administered. Toxicities should be evaluated using Version 3.0 of the NCI Common Toxicity Criteria.

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

1. Descriptive statistics should be used for reporting results.
2. Pharmacokinetic Substudy: A PK sub-study must examine capecitabine PK in children using accepted procedures and methods and will attempt to model important co-variates.

- **Labeling that may result from the studies:**

Any information to be included in labeling will depend on the results of the studies and discussions with FDA.

- **Format of reports to be submitted:**

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full datasets (including individual patient data listings), analysis, assessment, and interpretation. Even if the study fails, we need full study reports with data to support study conclusions. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. 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 should be used: Hispanic/Latino or Not Hispanic/Latino.

- **Timeframe for submitting reports of the study:**

  The study reports of the above studies must be submitted to the Agency on or before December 31, 2008. 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 your 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.

Submit reports of the studies as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling 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. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

As a reminder, you are responsible for compliance with section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002 by registering certain clinical trials in the Clinical Trials Data Bank (<http://clinicaltrials.gov/>) <<http://prsinfo.clinicaltrials.gov/) >>. If your drug is for the treatment of a serious or life-threatening disease or condition and you are conducting trials to test its effectiveness, then you must register the trials. Although not required, we encourage you to register trials for non-serious diseases. For additional information on registering your clinical trials, including the required and optional data elements, refer to the Protocol Registration System (PRS) Information Site (<<http://prsinfo.clinicaltrials.gov>>) and FDA's Guidances for Industry entitled "*Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*" (March 2002; revised draft January 2004).

If you have any questions, contact Carl Huntley, Regulatory Project Manager at 301-796-1372.

Sincerely,

Karen Weiss, M.D.
Deputy Director, Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

Karen Weiss

1/19/2007 08:07:28 AM