DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 3

NDA 020896

Hoffmann-La Roche Inc.
Attention: Lisa Chao, Ph.D.
Senior Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Chao:

Please refer to your correspondence dated April 15, 2010, requesting changes to FDA's March 17, 2005, Written Request for pediatric studies for capecitabine.

We also refer to your submission dated May 18, 2011.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 17, 2005, and as amended on January 19, 2007, and May 7, 2008, remain the same. (Text added is underlined. Text deleted is strikethrough.)

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

  1. In the Phase 1 portion of the study, ~~the PK sub-study will include approximately 9 patients in each of the following two age groups: age 3 years through 6 years and age 7 years through 12 years.~~ ~~W~~when the Maximum Tolerated Dose 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 17 will be enrolled~~ patients under the age of 18 will be enrolled. Forty-four patients are required for the final analysis of the phase 2 trial unless the trial is stopped for futility after 21 treatment failures have occurred. This total may include up to 10 patients from the phase 1 trial treated at the Maximum Tolerated Dose and who meet the same eligibility criteria for the phase 2 trial. The study protocol for the phase 2 study portion, addressing the issues outlined in this request, must be submitted to the Agency for review and agreement prior to study initiation. ~~Do not commence any study before FDA review of the protocol.~~

  3. The PK sub-study (which can be performed across phase 1 and phase 2) will include at least 9 patients in each of the following two age groups at time of enrollment: age under 6 years and age 7 years through 12 years.

- **Study endpoints:**

1. The primary purpose of the phase 1 portion of the study will be to determine the maxima~~l~~um 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~~. As the phase 1 objectives would be independent of type of glioma, patients with other types of malignant gliomas (e.g., high grade glioma) could be enrolled.

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 recent contemporary cooperative group historical controls will be performed. In addition, the study should provide a~~n assessment~~ description of the safety endpoints of the addition of ~~Xeloda®~~ capecitabine to brain radiation in this setting.

3. The PK sub-study will be achieved through secondary objectives of the phase 1 and phase 2 trials, i.e. 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.

- **Drug information:**

- *Dosage form:* Age appropriate formulation (e.g., 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~~ up to 14 weeks post completion of the radiation, with appropriate rest periods.

- *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. If appropriate, a biowaiver strategy could be used to address the relative bioavailability study.

- **Drug specific safety concerns:**

1. The safety and efficacy of capecitabine, a potential radiation sensitizer, 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. Effects of radiation should be monitored closely.

2. Safety evaluation 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 (or later) 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.~~

2. A single interim analysis for futility will be performed when the 21st failure is observed (includes failures of phase 1 patients treated at the MTD and who meet the same eligibility criteria for phase 2). Using the sequential probability ratio procedure, the regimen of capecitabine and radiation therapy will be considered ineffective and the trial will be closed to accrual if the nominal p-value at the interim analysis is > 0.2745. With this sequential design, the overall type 1 error rate is 0.1004 and the statistical power is 0.8997. If the trial is halted, the maximum probability that the decision would have been different had the targeted goal of 44 patients been treated and followed for at least one year is 0.005 (0.5%).

3. 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.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 17, 2005, as amended by this letter and by previous amendments dated January 19, 2007, and May 7, 2008, must be submitted to the Agency on or before September 30, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, 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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that capecitabine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Yolanda Adkins, Regulatory Project Manager, at 301-796-2850.

Sincerely,

{See appended electronic signature page}

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

Attachment (Complete Clean Copy of Written Request as amended)

NDA 020896 **WRITTEN REQUEST – AMENDMENT 3**

Hoffmann-La Roche Inc.
Attention: Lisa Chao, Ph.D.
Senior Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Dr. Chao:

Please refer to your Investigational New Drug Application (IND) for capecitabine. Reference is made to your proposed Pediatric Study Request submitted on November 1, 2004, for Xeloda (capecitabine, Ro 09-1978).

To obtain needed pediatric information on Xeloda, 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 Xeloda in the treatment of children with cancer.

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, 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, when the Maximum Tolerated Dose 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, patients under the age of 18 will be enrolled. Forty-four patients are required for the final analysis of the phase 2 trial unless the trial is stopped for futility after 21 treatment failures have occurred. This total may include up to 10 patients from the phase 1 trial treated at the Maximum Tolerated Dose and who meet the same eligibility criteria for the phase 2 trial. The study protocol for the phase 2 study portion, addressing the issues outlined in this request, must be submitted to the Agency for review and agreement prior to study initiation.

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3. 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.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical*

Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

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

  The study reports of the above studies must be submitted to the Agency on or before September 30, 2013. 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.

Reports of the studies that meet the terms of the Written Request dated March 17, 2005, as amended by this letter and by previous amendments dated January 19, 2007, and May 7, 2008, must be submitted to the Agency on or before September 30, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies 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 IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

If you wish to discuss any amendments to this Written Request, 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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505 A(e)(2), if:

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation in accordance with section 505A(e)(2).

- Under section 505A(j) of the Act, regardless of whether the studies demonstrate that capecitabine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies.

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Yolanda Adkins, Regulatory Project Manager, at 301-796-2850.

Sincerely,

{See appended electronic signature page}

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

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

/s/

RICHARD PAZDUR
07/01/2011