DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-087
IND 53,093

Hoffmann-La Roche, Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms DeVenezia-Tobias:

Reference is made to your correspondence dated June 27, 2003, requesting changes to FDA's March 1, 2000, Written Request for pediatric studies of Tamiflu® (oseltamivir phosphate).

We have reviewed the results of the juvenile animal toxicity studies. Based on these studies there is a concern for potential risk of central nervous system toxicity in younger infants. These infants may have an immature blood-brain barrier, and in consideration of the need to and difficulty of adequately monitoring CNS toxicity in this age group, we believe the drug should not be studied in infants less than 1 year of age. Therefore, we have removed the studies in neonates and infants less than one year of age. We are amending the sections listed below. All other terms in the Written Request dated March 1, 2000, remain the same.

Type of studies:

- Adequate and well-controlled study(ies) to evaluate the safety and clinical efficacy of oseltamivir to treat children with influenza.
- Assessment of safety of oseltamivir in adolescents.

Age group in which study will be performed:

- Efficacy data in children from one to twelve years of age
- Safety data in children one year of age through adolescence

Drug information

- Dosage form:
  - 30 mg/5 ml suspension and/or 60 mg/5 ml suspension (one to twelve years of age)
  - 75 mg capsule (twelve to seventeen years of age)

  There may be some overlap in age groups depending on the weight of the child and ability to swallow capsules.
- Route of administration: oral
- Regimen: to be determined

Clinical Endpoints:

For efficacy studies, time to alleviation of clinical symptoms (cough and nasal symptoms) and time to return to normal activity should be the primary endpoint. Cough, nasal symptoms and activity level should be captured using a validated scale. Duration of symptoms, extent or severity of symptoms and

incidence of defined secondary illnesses should be assessed. Use of concomitant medications for symptomatic relief and for secondary illnesses should also be tracked. Virologic endpoints should include proportion of study subjects with viral shedding during the follow-up period and duration of viral shedding.

Safety data should include an assessment of the potential for emergence of influenza virus resistant to oseltamivir and an attempt to characterize these strains if they are identified.

Statistical information, including power of study and statistical assessments*:*
Adequate numbers of children to detect clinically meaningful differences between treatment arms for confirmed influenza cases are required in the treatment efficacy studies. Analyses should include comparisons of primary endpoints between treatment groups using appropriate statistical methods including 95% confidence interval for relative treatment effect.

Safety analysis should be included for the intent-to-treat population (those with influenza-like illness), not only the population with confirmed influenza.

Labeling that may result from the study:
Appropriate sections of the label may be changed to incorporate the findings of the studies. The product label should be updated to reflect the sponsor's safety concerns in the less than 1 year age group and to include a summary of the juvenile animal toxicology data.

Timeframe for submitting reports of the study:
Reports of the studies should be submitted to the Agency on or before March 30, 2004. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Reports of the studies that meet the terms of the Written Request dated March 1, 2000, as amended by this letter must be submitted to the Agency on or before March 30, 2004, in order to possibly qualify for pediatric exclusivity under Section 505A of the Act.

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 you 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.

If you wish to discuss any further amendments to your Written Request as amended, please submit changes and the reasons for the proposed changes to your application. Submissions of proposed changes to your Written 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 your 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 to the pediatric population.

If you have any questions, please contact Sean J. Belouin, R.Ph., Regulatory Product Manager, at 301-827-2335.

Sincerely yours,

Edward Cox, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Edward Cox

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