DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-511/S-023
BLA 103964/5213

SUPPLEMENT APPROVAL

Hoffmann-La Roche, Inc.
Attention: Steven Toma, Pharm.D.
Associate Director, Pharma Development Regulatory
340 Kingsland Street
Nutley, NJ 07110

Dear Dr Toma:

Please refer to your Supplemental New Drug Application (sNDA) dated February 18, 2011, received February 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for COPEGUS® (ribavirin) 200 mg tablets and to your supplemental Biologics License Application (sBLA) dated February 18, 2011, received February 22, 2011, submitted under section 351 of the Public Health Service Act for PEGASYS® (peginterferon alfa-2a) 180 mcg/ml vial and 180 mcg/0.5 ml prefilled syringe.

We acknowledge receipt of your amendments to NDA 21-511/S-023 dated May 3, 2011, June 29, 2011, July 14, 2011 July 21, 2011, August 5, 2011, August 15, 2011, August 17, 2011. We also acknowledge receipt of your electronic correspondences submitted on August 18, 2011 and August 19, 2011.

We also acknowledge receipt of your amendments to BLA 103964 (b) (4) dated March 7, 2011 (3), May 3, 2011, June 28, 2011, July 14, 2011, July 21, 2011, August 5, 2011, August 15, 2011, August 17, 2011. We also acknowledge receipt of your electronic correspondences submitted on August 18, 2011 and August 19, 2011.

These Prior Approval supplemental new drug and biologics license applications were submitted to expand the indication for PEGASYS and COPEGUS combination therapy to include the treatment of chronic hepatitis C in patients 5 to 17 years of age and to update the Medication Guides with pediatric information.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)]/[21 CFR 601.14(b)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package inserts, Medication Guides), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)]/[21 CFR 601.12(f)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 2 years because there is evidence strongly suggesting that the drug products would be unsafe and necessary studies are impossible or highly impracticable in this pediatric group. PEGASYS® was previously judged to be contraindicated in neonates and infants because it contains benzyl alcohol.

We are deferring submission of your pediatric studies for ages 3 to 5 years for these applications because the product is ready for approval in patients 5 to 17 years of age and Copegus oral solution is not yet available for study in the 3 to 5 year age group.
Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported annually according to 21 CFR 314.81, 21 CFR 601.28, and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

For NDA 21-511/S-23 (COPEGUS®)

1811-1 Evaluate the safety, pharmacokinetics (PK), and antiviral effectiveness (as measured by sustained virologic response (SVR)) of Pegasys/Copegus combination therapy in pediatric patients by conducting an open-label, study of HCV-infected patients 3 to 5 years of age. The study must provide safety, PK and SVR data for at least 10 subjects 3 to 5 years of age who receive the Copegus oral solution formulation in combination with Pegasys. Analysis of safety, pharmacokinetics, and effectiveness should be conducted when all subjects in the 3 to 5 year age group have reached 24 weeks post-treatment, and these interim analyses should be submitted to FDA for review.

Final Protocol Submission:	04/2012
Interim Report Submission:	10/2019
Study Completion:	06/2022
Final Report Submission:	03/2023

For BLA 103964/5213 (PEGASYS®)

PMC-1 Evaluate the safety and antiviral effectiveness (as measured by sustained virologic response (SVR)) of Pegasys/Copegus combination therapy in pediatric patients by conducting an open-label, study of HCV-infected patients 3 to 5 years of age. The study must provide safety and SVR data for at least 10 subjects 3 to 5 years of age who receive the Copegus oral solution formulation in combination with Pegasys. Analysis of safety and effectiveness should be conducted when all subjects in the 3 to 5 year age group have reached 24 weeks post-treatment, and these interim analyses should be submitted to FDA for review.

Final Protocol Submission:	04/2012
Interim Report Submission:	10/2019
Study Completion:	06/2022
Final Report Submission:	03/2023

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA)/Biologics License Application (BLA) or as a supplement to your approved NDA and BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. Submit the October, 2019 Interim Report as a supplement to your

approved NDA and BLA or as a new NDA/BLA. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 5 to 17 years for these applications.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Pegasys was approved on October 16, 2002 and Copegus was approved on December 3, 2002, we have become aware of delayed growth in pediatric patients receiving Pegasys/Copegus, particularly long-term. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of delayed growth in pediatric patients receiving Pegasys/Copegus.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of delayed growth in pediatric patients receiving Pegasys/Copegus.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

For NDA 21511 (COPEGUS®)

1811-2 Collect long-term data related to effects of Pegasys/Copegus combination therapy on growth in pediatric patients 3 to 5 years of age enrolled in the open-label pediatric study. Long-term effects on other safety parameters should also be evaluated, including but not limited to hematologic abnormalities and thyroid function. Data on growth must be collected for a minimum of 3 years after completion of treatment.

The timetable you submitted on July 14, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2012
Trial Completion:	06/2022
Final Report Submission:	03/2023

For BLA 103964 (PEGASYS®)

PMC-2 Collect long-term data related to effects of Pegasys/Copegus combination therapy on growth in pediatric patients 3 to 5 years of age enrolled in the open-label pediatric study. Long-term effects on other safety parameters should also be evaluated, including but not limited to hematologic abnormalities and thyroid function. Data on growth must be collected for a minimum of 3 years after completion of treatment.

The timetable you submitted on July 14, 2011 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2012
Trial Completion:	06/2022
Final Report Submission:	03/2023

Submit the protocols to your IND, with a cross-reference letter to the NDA (for Copegus) and BLA (for Pegasys). Submit all final reports to your NDA and BLA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submissions, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required

will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]/21 CFR 601.12(f)(4),. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) and an approved BLA BLA (21 CFR 600.80 and 21 CFR 600.81).

If you have any questions, call Abiola Olagundoye, Pharm.D., Regulatory Project Manager, at (301) (301) 796-3982 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

DEBRA B BIRNKRANT
08/22/2011
I concur with this review.