CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125083Orig1s000

OTHER REVIEW(S)

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 4, 2004

FROM: Karen D. Winestock
Regulatory Project Manager
Division of Review Management and Policy, HFM-589
Office of Drug Evaluation VI

TO: STN 125083/0

SUBJECT: SBA Equivalent for:

- **Product: Peginterferon alfa-2a (PEGASYS) co-packaged with ribavirin USP (COPEGUS)**

  Manufacturer: Hoffmann-La Roche, Incorporated

- License Number: 0136

Indications and Usage

Peginterferon and ribavirin combination therapy was originally approved on December 3, 2002 for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with Interferon alfa. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

FDA's approval of biologics license application BL 125083 allows Hoffmann-La Roche to distribute a Peginterferon alfa-2a and ribavirin as a co-packaged product. The co-packaged product will be marketed under the trade name, PEGASYS® COPEGUS® Combination Pack.

Dosage Form, Route of Administration, and Recommended Dosage

- Peginterferon alfa-2a is for subcutaneous administration.

- Ribavirin is for oral use.

- **PEGASYS® COPEGUS® Combination Packs**
  The Combination Packs contain enough COPEGUS (ribavirin, USP) tablets and PEGASYS prefilled syringes to provide for four weeks of dosing. Each pack contains four single use, graduated, clear, glass prefilled syringes containing 180 µg of PEGASYS (peginterferon alfa-2a) in 0.5 mL of solution, four 27 gauge, ½ inch needles with needle stick protection device, four alcohol swabs and one bottle of COPEGUS 200 mg tablets for oral administration. The Combination Packs are available in the following configurations (identified by the prescribed daily dose of COPEGUS):

  800 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 112 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-17)

  1000 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 140 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-18).

  1200 mg COPEGUS® Daily Dose. This Combination Pack includes a bottle of 168 COPEGUS (200 mg) tablets, four PEGASYS prefilled syringes, and other components as listed above (NDC 0004-0353-39).

Basis for Approval
The following reviews, filed in the communication section of the license file for STN 125083/0, comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
Facility/CMC	Dr. Chiang Syin	December 10, 2003
Facility/CMC (Categorical Exclusion)	Dr. Chiang Syin	December 10, 2003
CMC/Product	Dr. Rao Kambhampati	March 19, 2004
Tertiary Review	Dr. Marc Walton	June 1, 2004

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Drug Evaluation and Research

DATE: June 3, 2004

FROM: Karen D. Winestock KDW
Regulatory Project Manager
Division of Review Management and Policy

TO: BL 125083/0

SUBJECT: FDA's June 2-3, 2004 Revised Package Inserts and Medication Guides

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Dr. Song called to discuss FDA's revised package inserts and Medication Guides. She noted that the date of the last revisions to the Peginterferon alfa-2a PI and Medication Guide had been changed from December 2003 to January 2004. I noted that although the FDA sent back the final approved version of the labeling in December 2003, the supplement was not approved until January 2004. As a result the date of the last revision should be consistent with the date of approval. Dr. Song understood and agreed to make the change.

Regarding the Copegus PI and Medication Guide that was faxed to Roche on June 3, 2004, Dr. Song noticed that a section under "How Supplied" had been omitted, and that the Medication Guide heading needed a few minor changes (lower case the r in ribavirin and capitalize all of the letters in tablets). I agreed to make the necessary changes and forward the revised labeling to Dr. Song.

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF NEW DRUGS

OFFICE OF DRUG EVALUATION VI

DIVISION OF REVIEW MANAGEMENT AND POLICY

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FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 10 **(Including Cover Page)**

FAX TO: Karen Song

Facsimile Telephone No. 973-562-3700 **Voice Telephone No.** 973-562-3812

FROM: Karen Krunestock

Facsimile Telephone No. 301-827-5397 **Voice Telephone No.** 301-827-4358

DATE: 1-23-04 **TIME:** 3:20 p.m.

MESSAGE: FDA's proposed carton + container labeling changes. Please confirm Receipt!

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FDA's 1-23-04 package and container labeling comments for BL 125083/0, PEGASYS® COPEGUS® (b) (4) Pack

1. The proprietary name PEGASYS® COPEGUS® (b) (4) Pack is not acceptable. However, PEGASYS® COPEGUS® Combination Pack would be acceptable. A letter will be sent to you regarding the FDA's decision.

2. Please make the following revisions to all of the package labels:

   a. On the top and front panels, increase the prominence of the proprietary and established names or decrease the prominence of the information that is found in the box. The prominence of the box also needs to be decreased.

   b. Include the dosage strength under the established name of each product
   PEGASYS® COPEGUS® (b) (4) Pack
   (Peginterferon alfa-2a) (ribavirin, USP)
   180µg/0.5ml 200 mg

   c. On the top panel, the proprietary and established names should precede the COPEGUS daily dose boxed information. Also see comments 1a and 1b.

   d. Reposition "For Subcutaneous Injection Only" so that it is clear this refers to just the Peginterferon alfa-2a. This can be accomplished by moving this information under the 4 Single Use Prefilled Syringes information or by moving (ribavirin USP) to the right and adding the word tablets underneath it.

   e. Include the usual dosage information for both products (e.g. PEGASYS 180µg/0.5 ml weekly dose, COPEGUS 800 mg daily dose) somewhere on the package label.

   f. Increase the prominence of the "Boxed Warning" regarding avoidance of pregnancy while taking this medication.

3. The COPEGUS container labels should include a usual dosage statement that is specific for the different containers (i.e., 800mg daily dose, 1000mg or 1200mg)

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: December 10, 2003

From: Chiang Syin, Ph.D., HFD-328, CDER/OC/DMPQ/TFRB

To: BLA File – STN 125083, Peginterferon alfa-2a co-packaged with Ribavirin, Hoffmann-La Roche Inc., U.S. License # 0136

Subject: Recommendation to waive a pre-license inspection

Indication: For the treatment of Hepatitis C

Through: Cynthia Whitmarsh, Acting Chief, CDER/OC/DMPQ/TFRB

Clearance Routing

CONCUR / DO NOT CONCUR Date: 12/11/03

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality, HFD-320
Office of Compliance
Center for Drug Evaluation and Research

CONCUR / DO NOT CONCUR Date: 12-19-03

Amy S. Rosenberg, M.D.
Director
Division of Therapeutic Proteins
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

cc: Kassa Ayalew, M.D., Committee Chair, OND/ODEVI/DTBIMP, HFM-582
Edwin Rivera-Martinez, Chief, OC/DMPQ/IPCB, HFD-322

Summary

Hoffmann La-Roche, Inc. (HLR) submitted a biologics license application on August 4, 2003, for the combination packaging of PEGASYS (peginterferon alfa-2a, BLA 103964) and COPEGUS (ribavirin, NDA 21-511) therapy for the treatment of chronic hepatitis C in adult patients with compensated liver disease not previously treated with interferon alfa. Currently the Pegasys BLA supplement (103964/5011) for the addition of prefilled syringes (PFS) dosage form is under review. The Agency has previously approved on December 3, 2002, under the STN 103964/5000 to allow Pegasys alone or in combination with Copegus, for the same indication. HLR did not propose to change the container-closure system of either licensed product. The primary and secondary packaging for Pegasys PFS remains unchanged; for Copegus, the primary packaging also remains the same. Both packaged products will be placed into a new carton (tertiary packaging for Pegasys PFS, secondary packaging for Copegus tablets) at HLR Nutley, NJ facility, resulting in only labeling changes for these combination packages. The Nutley facility also manufactures Copegus tablets.

The PEGASYS® COPEGUS® (b) (4) Pack provides a one-month supply of Pegasys PFS and Copegus. Each package contains a carton with 4 PEGASYS 180 mcg pre-filled syringes, a bottle of Copegus tablets (200mg/tablet), and package inserts/medication guide, as well as 4 needles and 4 alcohol swabs. The (b) (4) Packs are customized based on the requirement of different total daily ribavirin dose (1200, 1000, or 800 mcg of Copegus). HLR referred to the CMC information in the BLA 103964/0 and NDA 21-511.

Facility Information

PEGASYS® COPEGUS® (b) (4) Pack

Final packaging-HLR, Nutley, NJ.

PEGASYS

Peginterferon manufacturer- HLR, Nutley, NJ.
Peginterferon PFS manufacturer-F. Hoffmann-La Roche Ltd, Basel, Switzerland.
PFS packaging and warehousing – Kaiseraugst, Switzerland.
Final packaging, warehousing, distribution & final release testing – Nutley, NJ.

COPEGUS

Testing and releasing of drug substance – Basel, Switzerland.
Manufacturing, testing, packaging, and releasing of drug product; release, stability testing of packaged tablets; release testing of drug substance – Nutley, NJ.

The following lists the recent inspectional history of HLR facilities.

- Basel, Switzerland facility 11/2002 & 5/2003
- Nutley, NJ facility 5/2002 & 9/2003

The DMPQ reviewer, Carol Rehkopf, has recently completed a pre-approval inspection at HLR Switzerland facilities in May 2003 for the Pegasys prefilled syringe supplement (STN

103964/5011) and I have verified with Ms. Rehkopf that all objectionable observations from this inspection have been resolved.

Basis for Waiver

In accordance with CBER SOPP 8410, *Determining When Prelicense / Preapproval Inspections are Necessary*, an inspection is necessary when any of the following criteria are met:

1. **The manufacturer does not hold a U.S. license, or, in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.**
   HLR is the U.S. license holder of both PEGASYS® BLA (103964) and COPEGUS® NDA (21-511).

2. **FDA has not inspected the establishment in two years.**
   The most recent FDA inspection of HLR Switzerland facility for the Pegasys PFS occurred on May 19-24, 2003.

3. **The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.**
   I have verified with Ms. Rehkopf that all objectionable observations from the May 2003 pre-approval inspection have been resolved.

4. **The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.**
   There is no change in facilities.

5. **The manufacturing process is significantly different.**
   The manufacturing process remains the same. The only addition process is the final packaging of the convenience pack in Nutley, NY facility.

Recommendation

CDER has sufficient evidence gathered in other inspections and from the current submission to conclude that there is no impact on public health and HLR is in compliance with applicable regulations. I recommend to waive the pre-license inspection.

_____ Date: 12/10/03

Chiang Syin, Ph.D.
Therapeutic Facilities Review Branch, HFD-328
Division of Manufacturing and Product Quality
Office of Compliance

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Drug Evaluation and Research

DATE: September 25, 2003

FROM: Karen D. Winestock KDW
Regulatory Project Manager
Division of Application Review and Policy

Through: Kay Schneider, MS
Branch Chief
Division of Therapeutic Protein Products Branch

TO: BL 125083/0

SUBJECT: Filing Meeting

The filing meeting was held by e-mail on September 25, 2003. The reviewers from the Division of Antiviral Products found this submission acceptable for filing. During the first committee meeting, the reviewers from the Division of Clinical Trial Design and Analysis stated that the submission was acceptable for filing. On September 5, 2003, the DMPQ reviewer informed me that Hoffmann-La Roche needed to submit establish description information, however, the current application is acceptable for filing. DMPQ will not inspect the co-packaging site.