

**2. How does HLR plan to address the differences in container closures (size differences)?**

Prior to the filing of the NDA, HLR will draft a table to illustrate the differences, summarizing all stability packaging configurations, and submit it to the IND.

**3. DAVDP recommends that data on microbiological burden and moisture content of ribavirin tablets be included in the NDA.**

HLR will include these data in the NDA.

**4. Additionally, DAVDP would like to see a package listing batch analysis and impurity profiles that have been used in non-clinical studies. For this analysis, please list individual impurities (including unidentified impurities) separately, including the levels observed.**

HLR will supply this analysis.

APPEARS THIS WAY  
ON ORIGINAL

**RECORD OF INDUSTRY MEETING****Meeting Date:** October 20, 1999**Time:** 1:00 p.m.**IND:** 58, 827**Drug:** Ribavirin (Ro-9963)**Indication:** Treatment of Hepatitis C**Sponsor:** Hoffmann-La Roche, Inc.**Type of Meeting:** Discussion of Pharmacology/Toxicology Package for proposed NDA**FDA Participants:**

Therese Cvetkovich, M.D., Medical Team Leader, DAVDP  
Russell Fleischer, PA-C, M.P.H., Medical Officer, DAVDP  
David Morse, Ph.D., Pharmacology/Toxicology Reviewer, DAVDP  
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVDP  
Destry Sullivan, M.S., Regulatory Project Manager, DAVDP  
Anne Pilaro, Ph.D., Pharmacology/Toxicology Reviewer, CBER  
Victoria Tyson-Medlock, Consumer Safety Officer, CBER

**External Constituents:**

Loni da Silva, M.S., Global Regulatory Leader  
Mark Hope, Regulatory Associate  
Jennifer Dudinak, Pharm.D., Regulatory Associate  
Marlene Modi, Ph.D. Clinical Pharmacologist  
Celine Eliahou, Toxicologist

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**Background:**

Hoffmann-La Roche submitted its toxicology plans, dated August 9, 1999, for a future BLA/NDA for the PEGASYS/ribavirin combination for use in the treatment of patients with chronic Hepatitis C infection. This meeting was requested by Hoffmann-La Roche to discuss the suitability of these toxicology plans with both CDER and CBER reviewers and if possible, gain Agency concurrence to begin the proposed studies. For each discussion topic, the sponsor's position/question is shown in bold font, followed by the FDA's response in regular font.

**Discussion:**

*Hoffmann-La Roche seeks agreement/concurrence by the Agency on the following points:*

- 1. The toxicity of ribavirin is well documented in the literature; therefore, there should be no scientific or regulatory need to perform a complete toxicology program. This would be an unnecessary use of animals.**

The literature review submitted with the proposal in combination with the safety data from previously completed and ongoing clinical trials is adequate to address some of the DAVDP's concerns with respect to acute/repeat dose safety/tolerability of ribavirin. However, not all the data are acceptable, as some of the sites where these experiments were completed are not available for audit, or were audited in the past and found to be deficient (Specifically, the carcinogenicity studies conducted at \_\_\_\_\_ and the mouse testicular toxicity study conducted at the \_\_\_\_\_).

2. **A repeated dose toxicity study for pegylated interferon alfa-2a in combination with ribavirin is planned. This study will be done in monkeys, the most appropriate species.**

The proposed study is acceptable to the Agency. However, the Agency has some concern regarding the potential interpretability of this study, since both agents can cause organ specific histopathologic and biochemical injury to the liver, and the study design failed to include pre- and post-treatment liver biopsies for change score analysis.

3. **The effects of ribavirin in the areas of reproductive function, embryo-fetal toxicity, perinatal toxicity and mutagenic potential are well documented. There is no need to repeat these experiments, and a bibliographic submission should be sufficient.**

The proposal is not considered acceptable, as the NDA package would not contain adequately documented toxicology studies necessary to define the safety profile of the sponsor's ribavirin for the proposed "chronic use" indication (see item 1, above). Additional studies as outlined below will need to be conducted to characterize the toxicity and safety of the sponsor's ribavirin. Specific studies necessary would include:

- a) ICH guidelines state that three mutagenicity tests are required. Your proposal only includes one such study. The Agency requests that you conduct three mutagenicity tests (see Agency comments in point 5, below).
  - b) Segment I reproductive toxicology study(ies) addressing the time following ribavirin discontinuation before which pregnancy may safely be initiated. Both the safe initiation of pregnancy in females and the recovery of reproductive function in males after termination of ribavirin therapy must be demonstrated. (The Segment I open literature reference listed in your submission is not acceptable, as this study was audited and found to be deficient.)
4. **Would it be acceptable to label this combination as a category X drug (with respect to pregnancy) and would such labeling be acceptable as criteria for not conducting studies.**

Citations from the open scientific literature and the product label for Virazole aerosol (ribavirin) and Roferan are considered adequate to define the potential adverse effects of ribavirin and interferon on the developing fetus. It may be assumed that the combination drug product would receive the more restrictive labeling based upon the adverse effects demonstrated by any of its components. Therefore, the combination product could be labeled as category X based on the ribavirin safety data.

5. **Ribavirin is an established genotoxic agent. Information on the genotoxicity of ribavirin would be included in the label.**

The ICH guidelines call for the inclusion of a minimum of three genotoxicity assays (conducted under GLP conditions) to include at least:

- a) one *in vitro* bacterial cell assay
  - b) one *in vitro* mammalian cell assay
  - c) one *in vivo* mammalian assay.
6. Which assays would most fully satisfy the Agency's concerns regarding carcinogenicity studies? *(The sponsor has proposed not to conduct carcinogenicity studies, preferring to label their drug on literature genotoxicity data and the label for ribavirin aerosol.)*

Your proposal that the carcinogenicity work is complete is unacceptable. Studies the Agency would require include:

- a) A 2 year bioassay, in ~~(~~ the rat ~~)~~ ongoing at the time of the NDA submission.
  - b) A six-month carcinogenicity trial (the p53 knockout mouse study), which will be available for review at the time of the submission of the NDA.
7. Would phase IV commitments be acceptable to answer some of the pharm/tox concerns?

Completion of some pharm/tox studies as phase IV commitments, as indicated in our responses to your questions, will be acceptable. Specifically, completion of the 2 year bioassay in ~~the rat~~ would be acceptable as a phase IV commitment.

8. Hoffman-La Roche would like to see a detailed list of what each review division would like to see accomplished in regard to the split CBER/CDER review. There is a lack of consistency between the agency's review teams.

Both CDER and CBER review teams will work together to establish consistency in communications to Hoffmann-La Roche.

**Additional discussion points:**

- 1. Please clarify if you plan to submit the ribavirin product you are developing as a new or generic drug.

**Hoffman-La Roche intends to submit an application for ribavirin as a full NDA Under Section 505(b) of the Federal Food, Drug, and Cosmetic Act (the ACT).**

- 2. The Agency requested that Hoffmann-La Roche submit a table of contents for the proposed ribavirin NDA submission for review.

**Hoffman-La Roche will submit the requested table of contents for the proposed NDA submission.**

Signature, minutes prepared by: \_\_\_\_\_ Date: \_\_\_\_\_

**APPEARS THIS WAY  
ON ORIGINAL**

Concurrence:

HFD-530/MOTL/Cvetkovich  
HFD-530/MO/Fleischer  
HFD-530/Pharm Tox R/Morse  
HFD-530/Pharm Tox TL/Farrelly  
HFD-530/CPMS/DeCicco  
HFD-530/RPM/Sullivan

cc:

Original IND 58,827  
Division File  
HFD-530/MOTL/Cvetkovich  
HFD-530/MO/Fleischer  
HFD-530/Pharm Tox R/Morse  
HFD-530/Pharm Tox TL/Farrelly  
HFD-530/CPMS/DeCicco  
HFD-530/RPM/Sullivan

RECORD OF MEETING



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: November 26, 2002**

<b>To:</b> Jennifer Dudinak Duanne Voss	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, CMC comments	

**Total no. of pages including cover: 2**

**Comments:**

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**Document to be mailed: NO**

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** November 26, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530  
Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530

**NDA:** NDA 21-511

**Subject:** CMC Comments

With reference to your submission of NDA 21-511 for Copegus (ribavirin) Tablets, please address the following chemistry, manufacturing, and controls (CMC) comments and recommendations:

1. With regard to the ribavirin drug substance specifications, we agree with your initially proposed acceptance criteria for Specified Impurities \_\_\_\_\_, Total Unspecified Impurities, and Total Impurities but for the Individual Unspecified Impurities, we recommend a maximum of \_\_\_\_\_ which is based on the highest daily dose of ribavirin (1200 mg/day).
2. With regard to the Copegus Tablet specifications, we agree with your proposal for non-inclusion of \_\_\_\_\_. However, we recommend that you monitor it in the first \_\_\_\_\_ commercial stability lots of the drug product.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Destry Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 25, 2002

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Pregnancy Registry	

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**Total no. of pages including cover:** 9

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## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**Date:** November 21, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Rita Ouellet-Hellstrom, Ph.D., M.P.H., DDRE, HFD-430  
Dianne Kennedy, R.Ph, M.P.H., Pregnancy Labeling, Office of New Drugs,  
HFD-020  
Kathleen Uhl, M.D., Pregnancy Labeling, Office of New Drugs, HFD-020  
Karen Lechter, J.D., Ph.D., DSRCS, HFD-410  
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530  
Jeffrey Murray, M.D., Deputy Division Director, HFD-530  
Debra Birnkrant, M.D., Division Director, HFD-530

**NDA:** NDA 21-511

**Subject:** Pregnancy Registry for COPEGUS

---

The following comments pertain to your submission of a proposal for the pregnancy registry for ribavirin with respect to NDA 21-511:

### Background

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

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/s/

---

Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 5, 2002  
To: Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs  
Address: 340 Kingsland Street  
Nutley, NJ 07110-1199  
From: Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530  
Through: Rao Kambhampati, Ph.D., Chemistry Reviewer, HFD-530  
Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530  
NDA: NDA 21-511  
Subject: CMC Comments

With reference to your submission of NDA 21-511 for Copegus (ribavirin) Tablets, please address the following chemistry, manufacturing, and controls (CMC) comments and recommendations:

Drug Substance:

- 1) On the basis of the batch release and stability data for the primary/large scale batches of the ribavirin drug substance, we recommend the following changes to the acceptance criteria for            content and impurity contents in the proposed specification for ribavirin drug substance:

Test	Method	Roche's Proposed Acceptance Criteria	FDA Recommended Acceptance Criteria
<u>          </u>	USP Method <921>	Maximum <u>          </u>	Maximum <u>          </u>
Specified impurities:		Maximum <u>          </u>	Maximum <u>          </u>
		Maximum <u>          </u>	Maximum <u>          </u>
Unspecified Impurities:			
Individual		Maximum <u>          </u> each	Maximum <u>          </u> each
Total		Maximum <u>          </u>	Maximum <u>          </u>
Total impurities		Maximum <u>          </u>	Maximum <u>          </u>

- 2) For the Lots #990602 and 990615, the Total Impurities content and \_\_\_\_\_ content were decreased at the \_\_\_\_\_ time point in comparison to \_\_\_\_\_ time point after storage at 25°C/60%RH. Please provide an explanation for this phenomenon.
- 3) For the Lots #LW000910 and LW000911, the Total Unspecified Impurities Content and Total Impurities Content decreased at the \_\_\_\_\_ time point in comparison to the \_\_\_\_\_ time point after storage at 25°C/60%RH. Please provide an explanation for this phenomenon.
- 4) For Lot # 980611, significantly higher levels of the \_\_\_\_\_ were observed at \_\_\_\_\_ time points ( \_\_\_\_\_ comparison to initial, \_\_\_\_\_ time points ( \_\_\_\_\_ after storage at 25°C/60%RH. Please provide an explanation for this phenomenon.

**Drug Product:**

- 5) Several portions of the hand written notes in the Process Development Batch Record for the Lot# P001160 are not legible (N\_000\2002-05-01\cmc\riba\batch\p001160.pdf). Please provide a legible electronic or paper copy of the document, p001160.pdf.
- 6) The specifications for NDA registration batches contained \_\_\_\_\_ tests, however, the proposed Regulatory Controls for Copegus (ribavirin) Tablets (see NDA Drug Product Summary Section, pp 15, Table 8) did not include these tests. Please include these tests in the Regulatory Specifications.
- 7) On the basis of the batch release and stability data for the \_\_\_\_\_ batches of the ribavirin tablets, we recommend the following changes to the acceptance criteria for the determination of impurity contents and \_\_\_\_\_ the proposed specification for ribavirin tablets:

Test	Method	Roche's Proposed Acceptance Criteria	FDA Recommended Acceptance Criteria
Impurities	_____	Maximum _____	Maximum _____
Unspecified Impurities	_____	Maximum _____ each	Acceptable
Total Impurities	_____	Maximum _____	Acceptable
(%)	_____	<b>Not Proposed</b>	Maximum _____

- 8) In the majority of the \_\_\_\_\_ upon storage. Please provide an explanation for this phenomenon. If an internal investigation was already conducted, please provide a copy of the report.
- 9) The \_\_\_\_\_ batches (P001140, P001150, and P001160) that were manufactured by using \_\_\_\_\_ time point when stored at 25°C/60%RH or 30°C/60%RH but the primary batch #P002160 that was manufactured by using \_\_\_\_\_ time point. Please provide an explanation.

- 10) For the stability batch C194999/84's, at the \_\_\_\_\_ time point after storage at 25°C/60%RH and 30°C/60%RH \_\_\_\_\_ but at the 36 month time point \_\_\_\_\_ Please provide an explanation for this discrepancy.
- 11)
- 12) The \_\_\_\_\_ stability batches (P001140/1000's, P001150/1000's, P001160/42's, and P001160/1000's) had higher levels of \_\_\_\_\_ at the \_\_\_\_\_ time point ( \_\_\_\_\_ ) in comparison to the initial time point ( \_\_\_\_\_ ) after storage at 25°C/60%RH but those levels dropped at the \_\_\_\_\_ time point ( \_\_\_\_\_ ). Please provide an explanation.

**Copegus Bottle Labels:**

- 13) In the heading, please increase the prominence of the USAN name "(ribavirin)" by changing the letters in to bold font.
- 14) Please add "Tablets" after "(ribavirin)" in the heading.
- 15) Since Copegus Tablets bottle will not be co-packaged with Pegasys Injection vial, we recommend that you consider deleting " \_\_\_\_\_ "

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Destry Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 30, 2002**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Pregnancy Registry	

**Total no. of pages including cover: 5**

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** October 30, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530  
Jeffrey Murray, M.D., Deputy Division Director, HFD-530  
Debra Birnkrant, M.D., Division Director, HFD-530

**NDA:** NDA 21-511

**Subject:** Pregnancy Registry

---

The following comments pertain to your submission of a proposal for the pregnancy registry for ribavirin with respect to NDA 21-511:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

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S

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Destry Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 28, 2002**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Pregnancy Registry	

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**Total no. of pages including cover:** 3

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## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**Date:** October 28, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530

**NDA:** NDA 21-511

**Subject:** Pregnancy Registry

---

The following comments pertain to your submission of a proposal for a pregnancy risk management program for ribavirin with respect to NDA 21-511:

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3) Please provide this information no later than November 5, 2002.

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/s/

---

Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: October 21, 2002**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sillivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Clinical Pharmacology	

**Total no. of pages including cover:** 3

**Comments:**

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## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**Date:** October 21, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530  
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530

**NDA:** NDA 21-511

**Subject:** Clinical Pharmacology

---

The following comments pertain to your submission of NDA 21-511:

**Clinical Pharmacology:**

Please submit the following 2 electronic datasets:

1. Study 15801

Dataset that includes the following items for both treatment groups that received ribavirin (patients with PK data):

Patient #, weight, gender, age, serum creatinine (or creatinine clearance), ribavirin dose, treatment, week 12 and week 48 PK parameters (AUC, Cmax, Ctough).

2. Study 15492

Dataset that includes the following items (patients with PK data):

Patient #, weight, gender, age, serum creatinine (or creatinine clearance), ribavirin dose, ribavirin concentration at each week (4, 8, 12, 24, 48)

If you previously provided the above electronic datasets, please indicate the location.

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S

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Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 11, 2002

<b>To:</b> Jennifer Dudinak	<b>From:</b> Nitin Patel, R.Ph., Regulatory Project Manager for Destry Sillivan, MS
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Pharmacology comment	

**Total no. of pages including cover:** 2

**Comments:**

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** September 11, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Hao Zhang, Ph.D., Pharmacologist, HFD-530  
James G. Farrelly, Ph.D., Pharmacology Team Leader, HFD-530  
Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Medical Team Leader, HFD-530

**NDA:** 21-511

**Subject:** Pharmacology comment

---

The following Pharmacology comment is being conveyed to you on behalf of the review team regarding the 6-month P53 carcinogenicity study in mice (Roche Study No.: 07402; Vol.: 1 of 2; Pages: 1-832; in: NDA#21-511):

In your 6-month carcinogenicity study report in p53 (+/-) C57BL/6 mice with ribavirin (Re: Roche Study No.: 07402; Vol.: 1 of 2; Pages: 1-832), no historical control data were included regarding the tumor incidence rate in p53 (+/-) C57BL/6 mice. Please provide the available historical control data from the same testing facility using the same strain of mice to the reviewing division.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

15

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Nitin Patel, R.Ph. for Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation IV

---

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE: September 11, 2002**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Nitin Patel, R.Ph., Regulatory Project Manager for Destry Sillivan, MS
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Clinical Pharmacology comments	

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:** NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** September 11, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Kellie S. Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530  
Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Medical Team Leader, HFD-530

**NDA:** 21-511

**Subject:** Clinical Pharmacology comments regarding the pivotal BE study (NR16231)

---

The following Clinical Pharmacology comments are being conveyed to you on behalf of the review team regarding the pivotal BE study (NR16231).

As you note in Module I (page 45) of the report for the pivotal BE study (NR16231), 11 of 46 subjects had detectable pre-dose ribavirin concentrations in Period 1. This observation is not consistent with the required 6-month washout from ribavirin prior to study entry. Seven of the detectable pre-dose concentrations in Period 1 were higher than all of the detectable pre-dose concentrations in Period 2 that were due to the inadequate 15 to 18 day washout between doses.

1. Please repeat the statistical analysis for this study (point estimates and 90% confidence intervals for AUC and Cmax ratios) excluding these eleven subjects. Submit the results of this analysis as soon as possible, because they are critical for the NDA review.
2. Please provide a full description of your investigation into the explanation for the detectable pre-dose concentrations in Period 1.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/s/

---

Nitin Patel, R.Ph. for Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 25, 2002**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> NDA 21-511, Clinical Pharmacology	

**Total no. of pages including cover:** 3

**Comments:**

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**Document to be mailed:** NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** July 18, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Jooran Kim, PharmD., Clinical Pharmacology Reviewer, HFD-530  
Arzu Selen, Ph.D., Deputy Director, DPE III, HFD-880  
Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Medical Team Leader, HFD-530

**IND:** NDA 21-511

**Subject:** Clinical Pharmacology

---

The following comments pertain to your submission of NDA 21-511:

**Clinical Pharmacology:**

1. For Study NV15801, only  $C_{max}$  and AUC are provided in the datasets submitted. Please provide complete PK datasets that include all pharmacokinetic information (e.g.  $t_{1/2}$ ,  $V_d$ ,  $CL/F$ , etc).
2. The dissolution method for ribavirin tablets is not specified in the NDA submission. Please indicate if the dissolution method is the same as the method submitted under IND 58,827 (S-156), submitted March 26, 2002. If so, please submit this information to the NDA.

**APPEARS THIS WAY  
ON ORIGINAL**

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/s/

---

Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 29, 2002

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> IND 58,827, Clinical Pharmacology	

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:** NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** May 21, 2002

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Jooran Kim, PharmD., Clinical Pharmacology Reviewer, HFD-530  
Robert Kumi, Ph.D., Acting Clinical Pharmacology Team Leader, HFD-530  
Jules O'Rear, Microbiology Team Leader, HFD-530  
Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Steven Gitterman, M.D., Medical Team Leader, HFD-530

**IND:** 58,827 and NDA 21-511

**Subject:** Proposals for an NDA/BLA submission

---

The following comments pertain to your anticipated submission of NDA 21-511:

**Clinical Pharmacology:**

1. During the Pre-BLA/NDA meeting at CBER on May 3rd, 2002, you indicated that ribavirin pharmacokinetic information was obtained from the pivotal trials. Please submit a list of all the ribavirin pharmacokinetic information that was obtained. Please submit the PK/PD or population PK analyses that were performed with these data in the appropriate Human Pharmacokinetic/Clinical Pharmacology sections.

**Microbiology:**

2. Please discuss the proposed mechanism of action of ribavirin in light of the recent work from \_\_\_\_\_, laboratory.
3. Please provide a proposal for evaluating the development of resistance to ribavirin and to interferon, and discuss the implications of ribavirin mutagenicity on the development of resistance to pegylated interferon.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/s/

---

Destry Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation IV

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: November 27, 2001**

<b>To:</b> Jennifer Dudinak	<b>From:</b> Destry Sullivan
<b>Company:</b> Hoffmann-La Roche	Division of Antiviral Drug Products
<b>Fax number:</b> (973) 562-3554	<b>Fax number:</b> (301) 827-2471
<b>Phone number:</b> (973) 562-2930	<b>Phone number:</b> (301) 827-2335
<b>Subject:</b> IND 58,827, Final Study Report	

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**Total no. of pages including cover: 3**

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**Comments:**

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**Document to be mailed: NO**

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** November 21, 2001

**To:** Jennifer Dudinak  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russ Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Katherine Laessig, M.D., Acting Medical Team Leader, HFD-530

**IND:** 58,827, Serial Number 123

**Subject:** Proposals for an NDA/BLA submission

The following comments/requests pertain to serial number 123 and are being conveyed on behalf of Mr. Russell Fleischer: Please submit your responses to both CBER and CDER by December 7, 2001.

1. Please provide a proposed timeline for submission of a Pegasys/ribavirin NDA/BLA. Please include the proposed timing of a Pre-BLA/NDA meeting in the timeline.
2. Please provide a proposed table of contents for the application.
3. Please discuss the potential ramifications for a Pegasys/ribavirin application should the study comparing the various formulations of Pegasys demonstrate that the formulations are not bioequivalent.
4. Please provide your plans for studying pediatric patients who have chronic hepatitis C virus infection with Pegasys/ribavirin.

APPEARS THIS WAY  
ON ORIGINAL

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/s/

---

Destry Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products



IND 58,827

Hoffmann-La Roche Inc.  
Attention: Loni da Silva  
Program Director, Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Ms. da Silva:

Please refer to the meeting between representatives of your firm and the FDA on December 20, 2000. The purpose of the meeting was to discuss the suitability of Hoffmann-La Roche's Chemistry, Manufacturing, and Controls program for a future BLA/NDA for the PEGASYS/ribavirin combination for use in the treatment of patients with chronic Hepatitis C infection (Meeting Type B).

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Anthony W. DeCicco  
Supervisory Consumer Safety Officer  
Division of Antiviral Drug Products, HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** November 8, 2000

**To:** Barbara Kowal-Wilson  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, HFD-530  
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

**IND:** 58,827

**Subject:** Confirmation of the Investigator's Brochure for IND 58, 827, ribavirin.

---

The following comments are forwarded on behalf of Mr. Russell Fleischer:

It has come to our attention that there may be no Investigator's Brochure (IB) for your formulation of ribavirin. Further, we understand that you may be using the Rebetron™ Combination Therapy label in place of a formal IB for your ribavirin product.

Please provide the following:

1. The IB for your ribavirin.
2. If no IB exists, hard copies of the material(s) you provide to potential investigators that describe your formulation of ribavirin.
3. An annual report for your formulation of ribavirin.
4. Copies of all ribavirin safety-related communications you have provided to investigators since the inception of the clinical program.

Please provide this information no later than November 17, 2000.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

---

Destry M. Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products

**concurrency:**

HFD-530/MO/Fleischer.  
HFD-530/MTL/Cvetkovich  
HFD-530/RPM/Sullivan

**cc:**

HFD-530/Div. File —  
HFD-530/Orig. IND →  
HFD-530/MO/Fleischer.  
HFD-530/MTL/Cvetkovich  
HFD-530/RPM/Sullivan

## concurrency:

HFD-530/CTL/Miller, S.  
HFD-530/CR/Kambhampati, R.  
HFD-530/RPM/Sullivan

## cc:

HFD-530/Div. File —  
HFD-530/Orig. IND —  
HFD-530/MO/Fleischer  
HFD-530/CTL/Miller, S.  
HFD-530/CR/Kambhampati, R.  
HFD-530/MOTL/Cvetkovich  
HFD-530/RPM/Sullivan

Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration

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TELEFACSIMILE TRANSMISSION RECORD

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To: Barbara Kowal-Wilson  
Program Director, Drug Regulatory Affairs

Fax Number: (973) 562-3554

Date: October 2, 2000

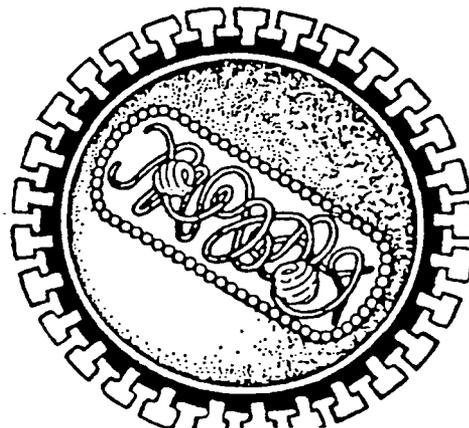
Company: Hoffman-La Roche

No. of pages (excluding cover): 1

Message:

CMC comment regarding serial number 035.

---



From: Destry Sullivan, M.S.  
Regulatory Project Manager, DAVDP

Telephone: (301) 827- 2335

Fax Number: (301) 827-2523

Mail:

Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
Rockville, Maryland 20857

Courier:

Division of Antiviral Drug Products  
HFD-530  
Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

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## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**Date:** March 16, 2000

**To:** Loni da Silva  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sullivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russ Fleischer, PA-C, M.P.H., Medical Officer, HFD-530  
Prabhu Rajagopalan, Ph.D., Clinical Pharmacology Reviewer, HFD-530  
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530  
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

**IND:** 58,827, Serial Number 006

**Subject:** Clinical Pharmacology comments regarding serial # 006. Please respond to the following requests/comments:

---

The following comments are forwarded on behalf of Dr Rajagopalan:

1. Please provide information regarding the excipients used and the manufacturing process employed in the production of lots C193518 and C194999. Also, please provide dissolution data for these two lots.
2. Please note that your drug development plan should include an assessment of the effect of food on the pharmacokinetics of ribavirin tablets.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

*DS*  
Destry M. Sullivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products

## concurrency:

HFD-530/MO/Fleischer

HFD-530/Biopharm TL/Reynolds

HFD-530/BiopharmR/Rajagopalan

HFD-530/MOTL/Cvetkovich

HFD-530/RPM/Sillivan

## cc:

HFD-530/Div. File 58,827

HFD-530/Orig. IND 58,827

HFD-530/MO/Fleischer

HFD-530/Biopharm TL/Reynolds

HFD-530/BiopharmR/Rajagopalan

HFD-530/MOTL/Cvetkovich

HFD-530/RPM/Sillivan



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** July 24, 2000

**To:** Loni da Silva  
Hoffmann-La Roche Inc.  
Program Director, Drug Regulatory Affairs

**Address:** 340 Kingsland Street  
Nutley, NJ 07110-1199

**From:** Destry M. Sillivan, M.S., Regulatory Project Manager, HFD-530

**Through:** Russ Fleischer, PA-C, M.P.H., Medical Officer, HFD-530  
Prabhu Rajagopalan, Ph.D., Clinical Pharmacology Reviewer, HFD-530  
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530  
Therese Cvetkovich, M.D., Medical Team Leader, HFD-530

**IND:** 58,827, Serial Number 026

**Subject:** Clinical Pharmacology comments regarding serial number 026, protocol 16231. Please respond to the following requests/comments:

---

The following comment is forwarded on behalf of Dr Rajagopalan:

- Please note that bioequivalence assessments should be based on  $C_{max}$  and  $AUC_{\infty}$ . According to Protocol NR16321 bioequivalence assessments will be based on  $C_{max}$  and  $AUC_{\tau}$ .

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/s/

Destry M. Sillivan, M.S.  
Regulatory Project Manager  
Division of Antiviral Drug Products

## concurrency:

HFD-530/MO/Fleischer

HFD-530/Biopharm TL/Reynolds

HFD-530/BiopharmR/Rajagopalan

HFD-530/MOTL/Cvetkovich

HFD-530/RPM/Sullivan

## cc:

HFD-530/Div. File 58,827

HFD-530/Orig. IND 58,827

HFD-530/MO/Fleischer

HFD-530/Biopharm TL/Reynolds

HFD-530/BiopharmR/Rajagopalan

HFD-530/MOTL/Cvetkovich

HFD-530/RPM/Sullivan

IND

Hoffmann-La Roche Inc.  
Attention: Loni da Silva  
Program Director, Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Ms. da Silva:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ribavirin (Ro 20-9963) for the Treatment of Hepatitis C.

We have completed the review of your application and have concluded that it is safe to proceed. In addition, please refer to the following comments and requests:

**Chemistry, Manufacturing, and Controls:**

*Please note that while similar comments were communicated under BB-IND we are providing further clarification of point six.*

1. In order to be consistent with the scientific literature, please use \_\_\_\_\_  
\_\_\_\_\_
2. From the \_\_\_\_\_ (Vol. 1.3, page 8), it appears that the \_\_\_\_\_  
\_\_\_\_\_ of \_\_\_\_\_ sample #980521 is \_\_\_\_\_ but the reported  
\_\_\_\_\_ is \_\_\_\_\_ Please provide an explanation for this discrepancy.
3. It was noticed that the \_\_\_\_\_ of the \_\_\_\_\_  
sample #980528 is slightly different from that of the USP Reference Standard. Please  
provide an explanation for the discrepancy.
4. Please compare the UV absorption spectrum of \_\_\_\_\_ sample with USP Reference  
Standard.
5. Please provide identity test specifications for reagents and solvents.
6. Please demonstrate the \_\_\_\_\_ of \_\_\_\_\_ by methods such  
as \_\_\_\_\_ We recommend that this be performed as a one-time test for each  
new supplier or new process for this starting material. Alternately, controls on  
\_\_\_\_\_ impurities in this starting material (other than at \_\_\_\_\_ could serve  
as surrogates for \_\_\_\_\_

7. In the specifications for \_\_\_\_\_, please include the assay and impurities content by methods such as \_\_\_\_\_.
8. In the specifications for \_\_\_\_\_ please determine the assay and impurities content by methods such as HPLC.
9. Please determine the specific rotation as according to the revised conditions published in the Ninth Supplement (page 4601) to USP 23. Accordingly, the test solution concentration should be 10 mg/mL in water and the specification for specific rotation should be -33.5° to -37.0°.
10. Please analyze the drug substance lots for the following expected impurities: \_\_\_\_\_ and, if detected, please include limits in the batch release and stability specifications.
11. Please provide a justification for not including the detection and quantitation of the following expected impurities in the HPLC analytical method for ribavirin drug substance: \_\_\_\_\_  
Please analyze some stability lots for these impurities and include the results in your justification. If appropriate, please amend the validation of the HPLC method accordingly.
12. In the stability protocol, please include a) testing at the \_\_\_\_\_ time point for the samples that are stored at 40°C/75%RH and b) a \_\_\_\_\_ test station for the samples stored at 25°C/60%RH.

**The following are related to ribavirin tablets:**

13. Please provide a statement indicating that the controls are in place to prevent contamination of \_\_\_\_\_ with \_\_\_\_\_.
14. Please analyze ribavirin tablets for the following expected degradation products: \_\_\_\_\_ and, if detected, please include limits in the batch release and stability specifications.
15. Please provide a justification for not including the detection and quantitation of the following expected degradation products in the \_\_\_\_\_ analytical method for ribavirin tablets: \_\_\_\_\_ Please analyze some stability lots for these degradants and include the results in your justification. If appropriate, please amend the validation of the \_\_\_\_\_ method accordingly.
16. Please evaluate the \_\_\_\_\_ of ribavirin tablets that are exposed directly to conditions such as 40°C/75%RH.

17. Since \_\_\_\_\_, could also be formed during the storage of ribavirin tablets, please monitor the stability lots for \_\_\_\_\_
18. In the stability study description, it was stated that the clinical batches of the ribavirin tablet bottles were closed with \_\_\_\_\_ child-resistant screw caps, however, in the tabulated data pages #63-64 (Vol. 1.4) it was indicated that the bottles are closed with \_\_\_\_\_ child-resistant screw-caps. Please clarify this discrepancy.
19. In the stability protocols for the drug product, please include \_\_\_\_\_ test station for the samples stored at 25°C/60%RH.
20. For the ribavirin tablets, please provide a justification for proposing Total Impurities content (HPLC) limit to a maximum of \_\_\_\_\_ for the initial lot release and a maximum of \_\_\_\_\_ for the stability testing.

As the sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder (Title 21 of the Code of Federal Regulations). These responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone no later than three working-days after receipt of the information, reporting reactions that are both serious and unexpected in writing within ten working days of receipt of the information (21 CFR 312.32) and submitting progress reports at least annually (21 CFR 312.33).

If you have any questions, please contact: Destry M. Sullivan, MS, Regulatory Management Officer at (301) 827-2335.

Sincerely yours,

/S/

Heidi M. Jolson, M.D.  
Director  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Concurrence:

HFD-530/Dir/Jolson

HFD-530/DepDir/Birnkrant

HFD-530/MOTL/Cvetkovich

HFD-530/CR/Fleischer

HFD-530/CTL/Miller

HFD-530/CR/Kambhampati

HFD-530/SCSO/DeCicco

HFD-530/RPM/Sullivan

cc:

Original IND 58,827

Division File

HFD-530/Dir/Jolson

HFD-530/DepDir/Birnkrant

HFD-530/MOTL/Cvetkovich

HFD-530/CR/Fleischer

HFD-530/CTL/Miller

HFD-530/CR/Kambhampati

HFD-530/SCSO/DeCicco

HFD-530/RPM/Sullivan

IND 58,827

SAFETY LETTER

IND 58,827

Hoffmann-La Roche Inc.  
Attention: Loni da Silva  
Program Director, Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Ms. da Silva:

Please refer to the meeting between representatives of your firm and the FDA on October 20, 1999. The purpose of the meeting was to discuss with both CDER and CBER reviewers the suitability of Hoffmann-La Roche's toxicology plans for a future BLA/NDA for the PEGASYS/ribavirin combination for use in the treatment of patients with chronic Hepatitis C infection (Meeting Type A).

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Destry M. Sullivan, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

/s/

Anthony W. DeCicco  
Supervisory Consumer Safety Officer  
Division of Antiviral Drug Products, HFD-530  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Concurrence:

HFD-530/CPMS/DeCicco

HFD-530/RPM/Sullivan

CC:

Archival IND 58,827

HFD-530/division file/TND 58,827

HFD-530/Dir/Jolson

HFD-530/Cvetkovich

HFD-530/Fleischer

HFD-530/Morse

HFD-530/CPMS/DeCicco

HFD-530/RPM/Sullivan

GENERAL CORRESPONDENCE (Minutes Sent)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved. OMB No. 0910-0297  
Expiration Date: February 29, 2004.

# USER FEE COVER SHEET

### See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p><b>Hoffmann-La Roche Inc.</b> 340 Kingsland Street Nutley, NJ 07110</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p><b>N021-511</b></p>
<p>2. TELEPHONE NUMBER (include Area Code)</p> <p>( 973 ) 562-2930</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____</p> <p>(APPLICATION NO. CONTAINING THE DATA.)</p>
<p>3. PRODUCT NAME</p> <p><b>COPEGUS™</b></p>	<p>6. USER-FEE I.D. NUMBER</p> <p><b>4335</b></p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (See Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of Information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Jennifer Dudinal</i>	TITLE Program Director	DATE May 31, 2002
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# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-511</u>	
Drug <u>COPEGUS™ (ribavirin) tablets for use in combination with the approved biologic product PEGASYS® (peginterferon alfa 2a)</u>	Applicant <u>Hoffmann-La Roche</u>
RPM <u>Destry M. Sullivan</u>	Phone <u>(301) 827-2379</u>
<input type="checkbox"/> 505(b)(1)	<input checked="" type="checkbox"/> Reference listed drug
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: Priority	
Pivotal IND(s) <u>58,827</u>	
Application classifications:	PDUFA Goal Dates:
Chem Class _____	Primary <u>December 3, 2002</u>
Other (e.g., orphan, OTC) _____	Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:  User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	Included
Original proposed labeling (package insert, patient package insert) .....	Included
Other labeling in class (most recent 3) or class labeling.....	Not included
Has DDMAC reviewed the labeling? .....	X Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels .....	Most recent included
Nomenclature review .....	Included
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application is **not** on the AIP.
  
- Exception for review (Center Director's memo)..... \_\_\_\_\_
- OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review) X Materials requested in AP letter
  
- ◆ Post-marketing Commitments Included in AP letter
  - Agency request for Phase 4 Commitments..... \_\_\_\_\_
  - Copy of Applicant's commitments ..... \_\_\_\_\_
  
- ◆ Was Press Office notified of action (for approval action only)?..... X Yeso
  - Copy of Press Release or Talk Paper..... \_\_\_\_\_
  
- ◆ Patent Included
  - Information [505(b)(1)] ..... \_\_\_\_\_
  - Patent Certification [505(b)(2)]..... \_\_\_\_\_
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... \_\_\_\_\_
  
- ◆ Exclusivity Summary ..... Included
  
- ◆ Debarment Statement ..... Included
  
- ◆ Financial Disclosure
  - No disclosable information ..... \_\_\_\_\_
  - Disclosable information – indicate where review is located ..... \_\_\_\_\_
  
- ◆ Correspondence/Memoranda/Faxes ..... Included
  
- ◆ Minutes of Meetings ..... Included
  - Date of EOP2 Meeting \_\_\_\_\_
  - Date of pre NDA Meeting \_\_\_\_\_
  - Date of pre-AP Safety Conference \_\_\_\_\_
  
- ◆ Advisory Committee Meeting ..... Held
  - Date of Meeting ..... November 14, 2002
  - Questions considered by the committee ..... \_\_\_\_\_
  - Minutes or 48-hour alert or pertinent section of transcript ..... \_\_\_\_\_
  
- ◆ Federal Register Notices, DESI documents ..... \_\_\_\_\_

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... X \_\_\_\_\_
  
- ◆ Clinical review(s) and memoranda ..... X \_\_\_\_\_

- ◆ Safety Update review(s) ..... N/A
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred  
Pediatric Page..... \_\_\_\_\_
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... N/A
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... N/A  
 Recommendation for scheduling ..... N/A
- ◆ Microbiology (efficacy) review(s) and memoranda ..... X
- ◆ DSI Audits ..... N/A  
 Clinical studies  bioequivalence studies ..... \_\_\_\_\_

**CMC INFORMATION:**

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

- ◆ CMC review(s) and memoranda ..... X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report) ..... N/A  
 Date completed \_\_\_\_\_  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

- ◆ Pharm/Tox review(s) and memoranda ..... X
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... X

APPEARS THIS WAY  
ON ORIGINAL