# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-511**

# ADMINISTRATIVE DOCUMENTS

Dennis P. Tramaloni
Senior Counsel & Managing Attorney

Roche

May 20, 2002

Food and Drug Administration
Division of Clinical Trial Design and Analysis
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
ATTN: DOCUMENT CONTROL CENTER, HFM-99
1401 Rockville Pike
Rockville, Maryland 20852-1448

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD 530
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL CENTER
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: Patent Rights Owned by Roche Relating to PEGASYS and Ribavirin

Check orange book

To Whom It May Concern:

The following patent applications pertinent in whole or in part to pegylated interferon alfa-2a, recombinant and/or ribavirin are owned by Hoffmann-La Roche Inc. and are presently pending in the United States Patent and Trademark Office:

1. United States Serial No. 06/256,204 for MICROBIAL PRODUCTION OF MATURE HUMAN LEUKOCYTE INTERFERONS;

2. United States Serial No. 07/145,002 for MICROBIAL PRODUCTION OF MATURE HUMAN LEUKOCYTE INTERFERONS;

3. United States Serial No. 09/255,948 for INTERFERON CONJUGATES; and

4. United States Serial No. 10/037,064 for METHOD OF TREATING HEPATITIS C INFECTION.

Applications Nos.1. and 2. include, inter alia, claims to recombinant alpha interferons and the DNA constructs encoding therefor. Application No. 3 includes claims to the branched pegylated interferon alfa-2a, recombinant (PEGASYS). Application No. 4 includes claims for the use of the combination of PEGASYS and ribavirin for the treatment of hepatitis C infection.

Very truly yours,

Dennis P. Tramaloni

118233

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199
Tel. 973-235-4475
Fax 973-235-2363
E-Mail dennis_p.tramaloni@roche.com

**Re: Pending NDA 21-511**

**COPEGUS™ (ribavirin) Tablets**

**Patent Information/Market Exclusivity Request**

Pursuant to the provisions of Section 505(c)(3)(D) and Section 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act ("Act") as amended, and to the provisions of 21 CFR 314(j)(4), we hereby claim a three (3) year market exclusivity period based upon the fact that new clinical investigations, which were conducted or sponsored by Hoffmann-La Roche Inc., were essential to the approval of the above Application. During this market exclusivity period, FDA may not make the approval of an application of the type described in Sections 505(b)(2) or (j) of the Act for the condition of approval of **COPEGUS** under the above NDA, effective before the expiration of three (3) years from the date of the approval of the above NDA.

In accordance with the further amendments to the Act, when the approval is made by the Food and Drug Administration, it is our understanding that this market exclusivity information will be included at the same time in the Approved Prescription Drug Product List ("Orange Book").

An updated Patent Information form is herewith attached.

APPEARS THIS WAY
ON ORIGINAL

## Market Exclusivity Certification

1. Pursuant to 21 CFR 314.50(j)(4), Hoffmann-La Roche Inc. ("Roche") certifies that to the best of its knowledge, the captioned Application contains "new clinical investigation(s)" that are "essential to approval" and were "conducted or sponsored" by Roche, as prescribed by 21 CFR 314.108(b)(4).

2. Roche certifies that, to the best of its knowledge, each of the clinical investigation(s) included in the Application is a "new clinical investigation" because it is an investigation in humans, the results of which (a) have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and (b) do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

3. Roche certifies that the new clinical investigation(s) in the captioned Application are "essential to approval " because there are no other data available that could support approval of the Application. Attached is a list of all published studies or publicly available reports of clinical investigations known to Roche obtained through a literature search that are relevant to the use of pegylated interferon alfa-2a / ribavirin tablets for which Roche is seeking approval.

4. Roche certifies that it has thoroughly searched the scientific literature and to the best of Roche's knowledge, the list is complete and accurate and in Roche's opinion, the published studies or publicly available reports (181 references) in the attached list do not provide a sufficient basis for approval of the conditions sought by Roche without reference to the new clinical investigation(s) in the captioned Application.

5. The studies or reports in the attached list are insufficient for the following reasons:

A. In references 14, 18, 33, 62, 119, 120, 121, 131, 150, citations of post-graduate courses, rather than clinical studies, are included.

B. In references 3, 110 non-English literature is quoted.

C. In references 24, 94 supplements, rather than original research, is referred to.

D. In References 47, 169, the publications presented were case reports.

E. In References 39, 64, 88, 105, 106, 113, 115, 162, there was no ribavirin studied in any treatment group

F. In References 2, 5, 6, 7, 8, 9, 11, 12, 13, 15, 16, 17, 19, 21, 22, 23, 25, 28, 29, 30, 32, 34, 35, 36, 37, 38, 40, 41, 43, 44, 45, 46, 47, 48, 49, 50, 53, 55, 61, 63, 66, 67, 68, 69, 70, 71, 75, 76, 77, 79, 80, 81, 82, 83, 84, 91, 92, 95, 96, 97, 98, 100, 103, 107, 108, 111, 114, 116, 117, 122, 123, 124, 125, 126, 127, 132, 133, 134, 135, 138, 139, 140, 141, 142, 143, 144, 145, 146, 148, 149, 151, 152, 153, 158, 159, 160, 163, 164, 167, 168, 170, 172, 175, 176, 177, 178, 179, 180, the publications represented review articles.

G. In References 20, 31, 54, 65, 66, 85, 86, 89, 99, 102, 104, 109, 112, 129, 130, 136, 137, 161, 165, 171, 173, 174, ribavirin capsules (Rebetol®, Schering Plough), not tablets were studied.

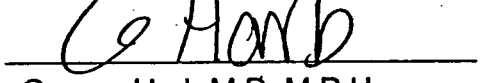
H. In References 1, 4, 26, 27,52, 166, the publications represented updates or newsletters.

I. In References 10, 51, 56, 57, 58, 59, 72, 73, 74, 78, 87, 90, 93, 101, 118, 147, 154, 156, 157, 181, ribavirin tablets were studied, however these were Roche-sponsored trials and the basis for the exclusivity request.

6. None of publications 5A. through 5H. addresses the clinical safety and efficacy of compounds administered in the form for which Roche is seeking approval for peginterferon alfa-2a / ribavirin tablets, as is required to produce labeling that adequately directs physicians and patients on the appropriate use of the peginterferon alfa-2a / ribavirin tablets.

7. Applicant, Roche, was the sponsor named in the Form FDA-1571 for IND No. 58827 under which the new clinical investigation(s) that were essential to the approval of the captioned Application were conducted.

Hoffmann-La Roche Inc



By: George Harb M.D.,M.P.H

Title: Medical Director

Date: October 7, 2002

## EXHIBIT A2

## PATENT INFORMATION FOR NDA NO. 21-511

| | | |
|---|---|---|
| 1) | Active Ingredient(s) | Ribavirin |
| 2) | Strength(s) | 200mg |
| 3) | Trade Name | Copegus |
| 4) | Dosage Form and Route of Administration | Tablets, Oral |
| 5) | Applicant (Firm) Name | Hoffmann-La Roche Inc. |
| 6) | NDA Number | 21511 |
| 7) | First Approval Date | Not yet approved* |
| 8) | Exclusivity: Date first ANDA could be approved | ANDA can not be approved for at least three (3) years from the date pending NDA is approved |
| 9) | Patent Information | See Attachment 2 |

## CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application Supplement has been approved.

## ATTACHMENT 2 TO EXHIBITS A1-A3

Based upon the NDA Applicant's present knowledge and belief, there are no patents which claim the drug or drug product or which claim a method of using the drug or drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed under the patent engaged in the manufacture, use, sale or import of the drug product that is the subject of this:

Choose one:

[X] New Drug Application No. 21-511

[ ] New Drug Application Supplement No. _____

By: _____
Dennis P. Tramaloni

Senior Counsel & Managing Attorney
Hoffmann-La Roche Inc.

October 4, 2002
Date

Rev 12/97

53268

**EXCLUSIVITY SUMMARY for NDA # 21-511 SUPPL #**
**Trade Name** COPEGUS™ **Generic Name** ribavirin
**Applicant Name** Hoffmann-La Roche **HFD-** 530
**Approval Date** December 3, 2002

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

   If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /__X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

   YES /X_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   3 years

   e) Has pediatric exclusivity been granted for this Active Moiety? Yes

YES /___/ NO /___/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #REBETOL (ribavirin), NDA 20-903

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or

available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #NV 15801

Investigation #2, Study # NV 15942

3. In addition to being essential, investigations must be "new"

to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not re-demonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study #NV 15801

Investigation #2, Study # NV 15942

4. To be eligible for exclusivity, a new investigation that is

essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 Study #NV 15801

IND # 58,827 and BBIND 7823 YES /_X_/ ! NO /___/ Explain:

Investigation #2, Study # NV 15942

IND # 58,827 and BBIND 7823 YES /_X_/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted

the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

151

Signature of Preparer Date 11/27/2002

Title: Regulatory Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

## PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA #NDA 21-511 Supplement # N/A Circle one:

HFD-530 Trade and generic names/dosage form: COPEGUS™ (ribavirin) 200 mg Tablets

Action: AP

Applicant Hoffmann-La Roche Therapeutic Class

Indication(s) previously approved: N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Proposed indication in this application: COPEGUS™ (ribavirin) 200 mg Tablets for the treatment of chronic hepatitis C virus infection in combination with PEGASYS® (peginterferon alfa 2a)

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __ Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) _Infants (1month-2yrs) Children (2-12yrs) _Adolecents (12-16yrs)

___ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

_3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes _X_No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer
(e.g., medical review, medical officer, team leader)

Destry Sillivan, M.S., Regulatory Project Manager
Signature of Preparer and Title

November 26, 2002
Date

cc: Orig NDA/BLA #
HFD- 530_____/Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

APPEARS THIS WAY
ON ORIGINAL


# DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** November 19, 2002

**TO:** Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
HFD-530

**VIA:** Destry Sillivan, Regulatory Management Officer, Division of Antiviral Drug Products
HFD-530

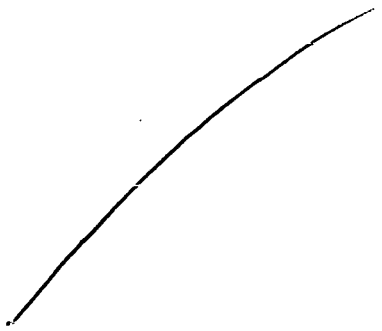
**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

**SUBJECT:** DSRCS Review of Patient Labeling for Copegus™ ( ribavirin) Tablets, NDA 21-511

The patient labeling which follows represents the revised risk communication materials for Copegus™ ( ribavirin) Tablets, NDA 21-511. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

During the review of the COPEGUS Medication Guide (MG), the following issues arose:



Comments to the review division are bolded, italicized, and underlined. Please let us know if you have any questions.

7 pages redacted from this section of the approval package consisted of draft labeling

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

/s/
---
Jeanine Best
11/19/02 01:20:17 PM
CSO

Toni, Please sign for Anne.

Toni Piazza Hepp
11/19/02 04:22:23 PM
PHARMACIST
for Anne Trontell

**MEMORANDUM** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 6, 2002

FROM: Rita Ouellet-Hellstrom, Ph.D., M.P.H., Epidemiologist
Division of Drug Risk Evaluation, HFD-430

THROUGH Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety, (ODS)

TO: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

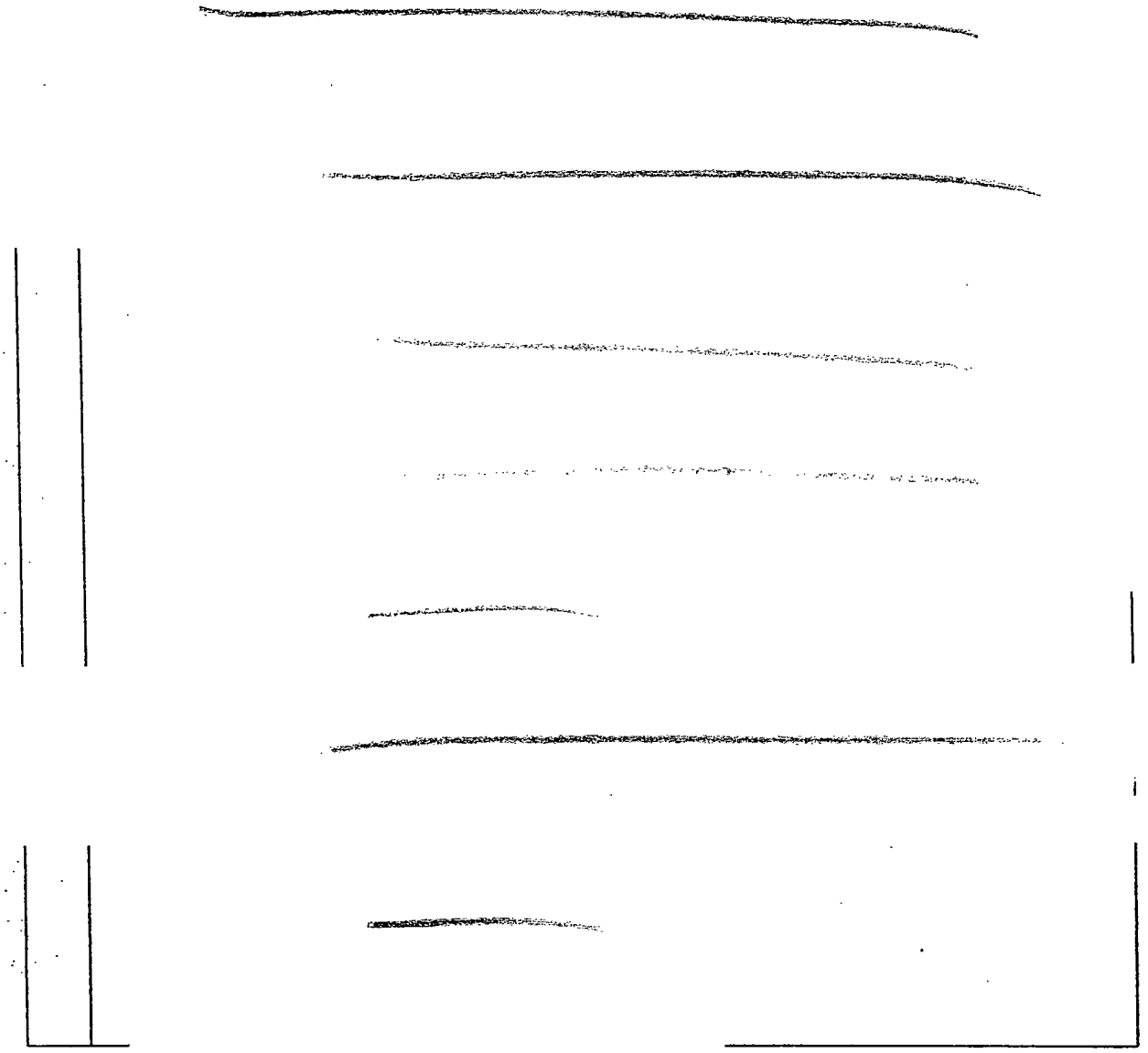
SUBJECT: ODS REVIEW
Review of Copegus® (ribavirin) Pregnancy Risk Management Protocol for Copegus® (ribavirin) Tablets
NDA Number: 21-511
PID Number: D020467

## EXECUTIVE SUMMARY

On October 21, 2002, the Division of Anti-Viral Drug Products (HFD-530) requested the Division of Drug Risk Evaluation (DDRE) to review and comment on the Hoffmann-La Roche, Inc. proposed Copegus® (ribavirin) Pregnancy Risk Management Program (RMP). This memorandum is in response to the consult.

The sponsor presents the information that will be included in the package insert for Copegus®, summarizes the components of the pregnancy prevention educational program, and describes the design to be followed in establishing the pregnancy registry. The registry design is based on the guidelines presented in FDA's *Guidance for Industry: Establishing Pregnancy Exposure Registries* announced on September 23, 2002.

WITHHOLD 9 PAGE (S)



## CONCLUSION

The Hoffmann-La Roche's Copegus® (ribavirin) Pregnancy Risk Management Program, as proposed, satisfies the legal requirement for labeling, education, and the establishment of a pregnancy registry. The program also provides a good foundation upon which to build a pregnancy registry that could potentially provide unequivocal answers on the toxigenic effects of ribavirin in humans. The protocol, however, fails to achieve its objectives as proposed. The sponsor is strongly encouraged to incorporate the suggestions presented in this evaluation, and to enlist the assistance of experts very early in the design phase. The program needs to be more focused. The activities need to be more precisely delineated and standardized. The data collection instruments need to be designed more objectively to collect the specific data items that will answer the teratogenic concerns.

/S/

Rita Ouellet-Hellstrom, Ph.D.
Epidemiologist

/S/

Mary Willy, Ph.D.
Epidemiologist

Concur: /S/

Julie Beitz, M.D.
Director

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

/s/
---
Rita Ouellet-Hellstrom
11/12/02 02:06:40 PM
UNKNOWN

Julie Beitz
11/13/02 12:18:05 PM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES

**MEMORANDUM**

**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

---

**DATE:** November 6, 2002

**FROM:** Karen Lechter, J.D., Ph.D.,
Division of Surveillance, Research, and Communication Support,
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support,
HFD-410

**TO:** Destry Sillivan, Project Manager, HFD 530

**SUBJECT:** DSRCS Comments on Copegus Pregnancy Registry
IND 58,827
NDA 21-511

We have reviewed the patient-oriented documents in Appendix 1 of the October 18, 2002 letter from the sponsor to Dr. Birnkrant and Dr. Weiss. We have the following comments.

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/s/
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Karen Lechter
11/6/02 12:04:53 PM
UNKNOWN

Anne Trontell
11/8/02 10:59:27 AM
MEDICAL OFFICER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 28, 2002

FROM: Dianne L. Kennedy, RPh, MPH and
Kathleen Uhl, MD
Pregnancy Labeling Team, OND, HFD-020

THROUGH: Sandra Kweder, MD
Deputy Director, OND, HFD-020

TO: Debra Birnkrant, MD
Director, Division of Antiviral Drug Products, HFD-530

SUBJECT: Review of Pregnancy Registry Protocol for
Copegus® (ribavirin) Tablets
BLA Number: 125061-0
NDA Number: 21-511

## I. EXECUTIVE SUMMARY:

Hoffmann-La Roche, Inc. has submitted a protocol for a voluntary, centralized pregnancy registry to systematically collect pregnancy exposure information related to the use of Copegus. The stated main objective of the registry is to "provide ongoing quantitative clinically relevant information about the outcomes of pregnancies exposed to Copegus." The protocol references the August 2002 "Guidance to Industry: Establishing Pregnancy Exposure Registries" however the protocol is fairly superficial and fails to address many important issues identified in the Guidance. The sponsor should be asked to develop and submit a more detailed protocol for the study.

This review by the Pregnancy Labeling Team is only a review of the Protocol for the Proposed Pregnancy Registry. We recommend that the Office of Drug Safety be consulted to provide a comprehensive assessment of the proposed Risk Management Program.

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## IV. CONCLUSIONS:

The protocol as written has several problems. The sponsor should be asked to address the issues outlined in this memo, review the Registry Guidance and resubmit a revised protocol. Due to time constraints for future meetings to discuss the pregnancy registry, this review does not cover an analysis of the proposed risk management program by Roche for this product. This review by the Pregnancy Labeling Team is only a review of the Protocol for the Proposed Pregnancy Registry. We recommend that the Office of Drug Safety be consulted to provide a comprehensive assessment of the proposed Risk Management Program.

S

Dianne L Kennedy, RPh, MPH

S

Kathleen Uhl, MD

Pregnancy Labeling Team

Cc:

| | |
|---|---|
| HFD-020 | Kweder, Kennedy, Uhl |
| HFD-530 | Birnkrant, Murray, Gitterman, Fleisher, Sillivan |
| ODS | Beitz, Trontell, Brinker, Hellstron, Lechter |
| CBER | Weiss, Weinstock |

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/s/
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Kathleen Uhl
10/29/02 03:36:35 PM
MEDICAL OFFICER

Sandra L. Kweder
10/30/02 01:45:40 PM
MEDICAL OFFICER

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | **REQUEST FOR CONSULTATION** |
|---|---|

| *Division/Office)*: ODS Attn: Julie Beitz, M.D. and Quynh Nguyen | | | FROM: DAVDP- HFD-530 | |
|---|---|---|---|---|
| ..TE:10/212002 | IND NO.:58,827 | NDA NO.: 21-511 | TYPE OF DOCUMENT : | DATE OF DOCUMENT: 10/21/2002 |
| NAME OF DRUG:<br>Copegus (ribivirin) | PRIORITY CONSIDERATION:<br>priority | | CLASSIFICATION OF DRUG: antiviral, anti-hepatitis C | DESIRED COMPLETION DATE: Nov 15, 2002 |

NAME OF FIRM: Bristol-Myers Squibb

## REASON FOR REQUEST

### I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
X SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
X OTHER *(SPECIFY BELOW)*: X

### II. BIOMETRICS

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER: | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER: |

### III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

| X CLINICAL | ☐ PRECLINICAL |
|---|---|

COMMENTS/SPECIAL INSTRUCTIONS: DAVDP requests that you review Hoffman La-Roche's ribavirin pregnancy risk management program, which includes a pregnancy registry. Their proposal will be forwarded to you as a Word attachment over email, and can be mailed to you as well. Please forward DAVDP the name of the reviewer you assign as soon as possible, as we are having an internal meeting to discuss their proposal on Monday, October 28, 2002. Please also note that the PDUFA goal date for this application is December 3, 2002.

| SIGNATURE OF REQUESTER:<br>Destry M. Sillivan | METHOD OF DELIVERY (Check one):<br>MAIL ☐ HAND X EMAIL |
|---|---|
| SIGNATURE OF RECEIVER: | SIGNATURE OF DELIVERER: |

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/s/

Destry Sillivan
10/23/02 10:27:10 AM

# MEMORANDUM

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

**DATE:**

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

**TO:** Clinical Trials Minutes File

**SUBJECT:** BB-IND 7823

---

**Meeting Date:** May 7, 2002 **Time:** 2:30 to 4:30 p.m.

**Location:** WOC 1, Conference Room 1

**Sponsor:** Hoffmann-La Roche

**Type of Meeting:** PreBLA/NDA

**Meeting Objectives:** To present and discuss data from pivotal trials, NV15801 and NV15942, that support the BLA/NDA filing; and to obtain concurrence that the overall benefit-risk profile and scope of the data in the Phase 3 pivotal trials justify fast-track designation and priority review for the BLA/NDA

**Product:** Pegylated Interferon alfa-2a (human, recombinant, *E. coli,* Hoffmann-La Roche) and Ribavirin

**Clinical Indication:** Treatment of chronic hepatitis C

**FDA/CBER Attendees:** Karen Weiss, Mark Thornton, Martin Green, Anne Pilaro, Jawahar Tiwari, Ghanshyam Gupta, Earl Dye, Karen Winestock, Glen Jones, Kay Schneider, James Reese, Raymond Joseph, Carol Rehkopf, Jose Tavarez-pagan, Bradley Glasscock, Michael Fauntleroy, Sherry Lard-Whiteford, and Emanuel Petricoin (by telephone)

**FDA** Tracey Forfa

| | |
|---|---|
| **CDER Attendees:** | Debra Birnkrant, Narayana Battula, Anthony DeCicco, James Farrelly, Russell Fleischer, Rao Kambhampati, Jooran Kim, Steven Gitterman, Fraser Smith, Jules O'Rear, David Roeder, Destry Sillivan, Guoxing Soon, Hao Zhang and James Morrison |
| **Sponsor Attendees:** | Michael Brunda, Cynthia Dinella, Jennifer Dudinak, Joe Hoffman, Amy Lin, Marlene Modi, Mary Ellen Mulligan, Chris Pappas, Hagen Pfundner, Adrian DiBisceglie, Candice Teuber, Celine Eliahou, Kathleen Schostack, and Frank Duff |

**Introduction**

The meeting began with an introduction by Hoffmann-La Roche. Hoffmann-La Roche has been developing Pegylated Interferon alfa-2a alone and in combination with Ribavirin for the treatment of chronic hepatitis C. Pegylated Interferon alfa-2a and Ribavirin combination therapy has been approved in other countries and the sponsor is now ready to submit a BLA/NDA for marketing in the United States. The sponsor has completed two Phase 3 pivotal trials (studies NV15801 and NV15942) that were designed to address unmet medical needs within the hepatitis C community. The purpose of this meeting was to discuss the data from the two Phase 3 trials and obtain FDA concurrence on content, format, and review status of the pending applications.

**Clinical Questions**

1. **Does FDA concur that the pivotal studies achieved their objectives?**

   - **NV15801: Demonstrated superiority in efficacy (sustained virological response, SVR) of Pegasys and Ribavirin combination therapy over Rebetron**

   - **NV15942: Evaluated prospectively the individualization of treatment duration (24 vs. 48 weeks) and Ribavirin dose (800 mg fixed dose vs. 1000 or 1200 mg by body weight categories) according to pretreatment HCV genotype and viral load**

   Based on the data submitted in the briefing package, CBER stated that the studies appeared to be successful. However, a definitive response could not be made until the data have been thoroughly reviewed.

2. **Does FDA agree to sustained virological response (SVR) as the primary efficacy endpoint, as presented in the Pre-BLA/NDA meeting package, for inclusion into the Clinical Studies section of the USPI and to support approval of Pegasys and Ribavirin combination therapy?**

Based on pr[illegible] discussions with CBER, the use of SVR as the primary efficacy endpoint is acceptable, however comments related to labeling could not be addressed at this time.

CDER asked for the rationale behind the change and when the change was made.

*The sponsor stated that after the Antiviral Committee Meeting held in December 2001 it became clear that the use of SVR alone as the primary endpoint would be acceptable.*

CBER added that at the time the protocols were initiated, the Agency believed that the use of two coprimary endpoints was more appropriate than SVR alone. At the time, there was not a lot of knowledge about clearance of SVR and what it truly meant in this patient population.

3. **Base upon the results from NV15942, does FDA concur with the recommendation of treating genotype non-1 patients with Pegasys plus Ribavirin combination therapy for 24 weeks using an 800 mg dose of Ribavirin?**

The FDA stated that this question could only be addressed after the data have been thoroughly reviewed.

4. **Does FDA concur that the pivotal Phase III trials NV15942 and NV15801 have satisfied several of the key unmet medical needs identified at the FDA Antiviral Drugs Advisory Committee meeting on December 12, 2001?**

Specifically:

- **Clear determination of patient groups (e.g., genotype, viral titer) in which combination treatment with Pegylated Interferons is superior to combination treatment with Interferon.**

- **Optimum duration of treatment (i.e., 24 weeks instead of 48 weeks) in patients with a high likelihood of response (e.g., genotype non-1). In order to avoid the added toxicity of longer treatment without compromising efficacy.**

- **Prospectively evaluated Ribavirin dose for patient subgroups (i.e., genotype 1 and non-1).**

The FDA agreed that study NV 15942 addresses some of the key unmet medical needs identified at the FDA Antiviral Drugs Advisory Committee meeting held on December 12, 2001. CBER has not sought to remove the fast track designation. However, CBER does not believe that each of the comments listed above support a priority review designation.

**5a. Does FDA concur that based upon the data from NV15801 Pegasys and Ribavirin combination therapy is superior to Rebetron, the standard of care for the treatment of hepatitis C?**

**5b. Does FDA concur that the Pegasys and Ribavirin efficacy data are confirmed in NV 15942?**

**5c. Does FDA concur that this efficacy benefit over Rebetron is maintained in the patient subgroups (genotype 1 [both low viral load and high viral load] and genotype non-1)?**

In response to questions 5a, 5b and 5c, CBER stated that a thorough review of the data would need to be performed before these questions could be addressed.

**6. Does FDA concur that the overall benefit-risk profile and scope of the data from the Phase III trials, NV15801 and NV15942, justify the filing and ultimate approval of a BLA/NDA?**

CBER stated that after reviewing the table of contents, it appears that the appropriate studies have been performed to justify the filing of a BLA, however the data will need to be reviewed before a definitive answer could be given regarding the filing and approval status of the applications.

**7. Does the FDA concur that the overall benefit-risk profile and scope of the data in the Phase III pivotal trials justify maintaining fast-track designation and receiving priority review for the BLA/NDA?**

As stated in response to question 4, CBER has not sought to rescind fast track designation for IND 7823. CBER is strongly considering granting the Pegylated Interferon alfa-2a and Ribavirin BLA/NDA priority review status, but a final decision will not be made until the application has been received. The sponsor should note that FDA does not agree with all the justifications given regarding why priority review status should be given to the application.

**8. Does CBER envision a FDA Advisory Committee meeting to discuss this application?**

CBER and CDER stated that they are considering bringing this application to an Advisory Committee. The polling of committee members has been initiated. However, due to the potential short review clock (6-months), scheduling and review concerns will ultimately determine if a committee meeting can be scheduled.

**9. Does FDA have any further requests or recommendations for the BLA/NDA filing?**

The sponsor was informed that the full user fee would be needed for the BLA. CDER agreed to confirm the user fee for the NDA but believed that one-half the normal fee would be needed.

- CDER requested a subsequent telephone conference be scheduled to discuss the need for a pregnancy registry, microbiology issues, and the Ribavirin pharmacology/toxicology data. CDER would be responsible for setting-up the meeting and agreed to submit a list of questions to the sponsor prior to the meeting date.

- CBER inquired about the status of the second version of the electronic demo.

  *The sponsor stated that their response would be sent by May 8, 2002.*

**Pending Format, Content and Administrative Handling Questions**

1. **Does FDA concur with the Sponsor's proposed format and content for the BLA/NDA?**

   - **Annotations: As was previously agreed for the original BLA 103964/0, the Sponsor proposes to annotate only the package insert of the BLA/NDA.**

     CBER stated that all labeling should follow the January 1999 Guidance document.

   - **Resubmission of the final study report from BLA 103964/0: For the reviewer's convenience, the Sponsor proposes to resubmit the final study report for protocol NV15800 that was provided as part of the original BLA 103964/0.**

     CBER found this proposal acceptable.

   - **Combined Human Pharmacokinetic and Biopharmaceutics/Clinical Pharmacology Summary: As was previously agreed for the original BLA103964/0, the Sponsor proposes that the Human Pharmacokinetic and Biopharmacokinetics Summary and Clinical Pharmacology Summary be combined into a single summary. Please refer to Appendix 1 (TOC for Proposed Combined Human Pharmacokinetic and Biopharmaceutics/Clinical Pharmacology Summary).**

     CBER found this proposal acceptable.

   - **Proposals for ISS and ISE (refer to Attachments 7 & 8)**

     CBER found this proposal acceptable.

**In addition to the proposals outlined above, the Sponsor would also welcome any feedback from the FDA on additional format and content issues that the Agency would like the Sponsor to address while preparing the BLA/NDA submission.**

CDER requested the sponsor submit data from any dose ranging pharmacokinetic (PK) studies conducted using Ribavirin (i.e. with relevant doses used in the clinical studies) be submitted with the BLA/NDA.

2. **Does the FDA concur with the Sponsor's proposal to physically consolidate all data that are common to both the BLA and NDA into a single BLA/NDA submission?**

   - **Given that the common clinical and preclinical databases will support marketing approval of the two components of the combination treatment, the Sponsor proposes to physically consolidate all of its data into a single BLA/NDA submission, i.e. the BLA and NDA would contain identical components in each section of the application with the exception of section 4. CDER would receive only the CMC information for Ribavirin. CBER would receive the CMC information for Pegasys.**

     The FDA found this proposal acceptable.

3. **Does FDA have any advice on administrative handling and communication between the Sponsor and CBER and between the Sponsor and CDER for the combined review of the BLA/NDA submission?**

   - **Primary contact for questions during review: Based on the designation of jurisdiction letter it is the Sponsor's understanding that CBER will be the principal contact point during the course of the review, including labeling negotiations.**

     CBER informed the sponsor that the regulatory project manager (RPM) would be the primary contact for issues related to the combination therapy BLA. The CDER RPM will be the primary contact for issues related to the Ribavirin NDA (CMC and preclinical)

   - **Notification to Sponsor on fileability: Based on the designation of jurisdiction letter it is the Sponsor's understanding that CBER will notify the Sponsor on fileability of the application.**

     The FDA stated that if CBER and CDER deem the BLA and NDA submissions fileable, CBER would be the only agency issuing a filing letter. However, since the applications are dependent on each other, if one agency finds deficiencies in their application, both CBER and CDER will issue a refusal to file letter.

- **Notification to Sponsor on action date: Based on the designation of jurisdiction letter it is the Sponsor's understanding that both CBER and CDER will separately provide an action letter to the Sponsor. It is also the Sponsor's understanding that this process will be coordinated in terms of timing and response.**

  The FDA stated that both agencies will issue separate action letters and that the timing and responses would be coordinated.

- **The Sponsor is seeking trade name designation for the convenience kit package and Ribavirin. The Sponsor was advised by Ms. Winestock to formally submit a request for trade name designation for Ribavirin to CDER. The formal request for trade name review was sent to CBER and CDER on March 15, 2002. Could the Agency please comment if any additional steps need to be taken by the Sponsor to ensure trade name designation is provided prior to the approval of Pegasys and Ribavirin combination therapy.**

  CBER stated that the trade name review request for Pegylated Interferon and Ribavirin combination therapy had been received by CBER and is currently under review in the Advertising and Promotional Labeling Branch (APLB). CBER stated that comments could possibly be sent to the sponsor by the end of May. CDER stated the request for the trade name review for Ribavirin had been sent to Ms. Sammie Beams, Office of Drug Safety (ODS). A decision would probably be made in 60 days. The sponsor should contact Ms. Beam, ODS, directly, or Mr. Sillivan for status updates.

4. **The Sponsor proposes to provide the 4-Month Safety Update on August 30, 2002 with a clinical cut-off date of May 2002. Does the FDA concur?**

   The FDA requested the sponsor provide the agencies with a list of the studies and summary data that will be used to provide the safety update. After reviewing the data, the Agencies would provide final comment on the acceptability of this proposal.

5. **Does FDA concur with the Sponsor's proposals for CRT's and Data sets: Item 11?**

   - **The sponsor plans to submit Case Report Tabulations (patient profiles and data sets) for the two pivotal phase III trials (NV15801 and NV 15942) in accordance with the Guidance, "Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format". Does the Agency concur?**

     CBER found this proposal acceptable. However, CDER requested the sponsor only submit the PK data and adverse event data sets for the Ribavirin treated patients. The

Ribavirin patient profile data would not be needed. In addition, adverse event information from all Ribavirin PK studies should be submitted in addition to the listed data sets.

- **The Sponsor proposes not to submit patient profiles for the clinical pharmacology studies, but to submit the following data sets: bioanalytical results for each analyte (PEG-IFN alfa-2a and ribavirin) and pharmacodynamic marker (serum 2', 5'-OAS activity) derived pharmacokinetic and pharmacodynamic parameters subject demography information for each study.**

  The FDA found this proposal acceptable.

6. **Does FDA concur with the Sponsor's proposal for CRF's: Item 12?**

   **The sponsor will provide CRF's for deaths and dropouts due to adverse events and lab abnormalities for all studies submitted in the filing. For the ongoing studies included in the "Safety Data from Other Trials" section of the ISS, Roche proposes to not submit CRF's since the studies are ongoing and the databases are not closed.**

   The FDA found this proposal acceptable.

7. **Does FDA concur with the Sponsor's proposal to cross-reference the combination BLA/NDA to BLA 103964-0 (original submission and responses to the CR Letter, including CMC BLA Update Section)?**

   CBER stated that the proposal to cross reference the monotherapy BLA was acceptable. The sponsor should note that if there were a problem with the monotherapy BLA data, such as the CMC data or clinical pharmacology comparability data that would warrant the issuance of another complete response letter, it would also affect the combination BLA. However, if the problem were unique to the monotherapy application, such as certain clinical or preclinical data that had no bearing on combination use, the Agency would work with the Sponsor to manage the problem and minimize the impact on the combination BLA.

8. **The Sponsor proposes to provide in section 4 of the BLA for CBER only Pegasys technical information. The Sponsor proposes to provide in section 4 of the NDA only Ribavirin technical information. Does FDA concur?**

   The FDA found this proposal acceptable.

**ACTION ITEMS**

- If the original submission is filed electronically, all subsequent submissions amending the original application should also be submitted in electronic format in accordance

with the document titled, "Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) - Biologics Marketing Applications.

- The FDA will determine whether a Medication Guide is needed for the convenience pack.
- The Sponsor will submit the second version of the electronic demo by May 8, 2002.
- CDER will schedule a follow-up telephone conference to discuss the Ribavirin PK data and the pregnancy registry.

The sponsor plans to submit the BLA/NDA on June 7, 2002.

The meeting adjourned.

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

# REQUEST FOR CONSULTATION

| | | | | |
|---|---|---|---|---|
| TO (*Division/Office*)<br>Sammie Beam<br>OPSS/DMETS, HFD-400 | | | FROM:<br>Destry M. Sillivan, RPM, DAVDP, HFD-530 | |
| DATE<br>May 3, 2002 | IND NO. | NDA NO. | TYPE OF DOCUMENT<br>General Correspondence | DATE OF DOCUMENT<br>March 15, 2002 |
| NAME OF DRUG<br>ribavirin | | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>Antiviral | DESIRED COMPLETION DATE<br>July 5, 2002 |

NAME OF FIRM
Hoffmann-La Roche, Inc

REASON FOR REQUEST

I. GENERAL

| | | |
|---|---|---|
| 9 NEW PROTOCOL | 9 PRE-NDA MEETING | 9 RESPONSE TO DEFICIENCY LETTER |
| 9 PROGRESS REPORT | 9 END OF PHASE II MEETING | 9 FINAL PRINTED LABELING |
| 9 NEW CORRESPONDENCE | 9 RESUBMISSION | 9 LABELING REVISION |
| 9 DRUG ADVERTISING | 9 SAFETY/EFFICACY | 9 ORIGINAL NEW CORRESPONDENCE |
| 9 ADVERSE REACTION REPORT | 9 PAPER NDA | 9 FORMULATIVE REVIEW |
| 9 MANUFACTURING CHANGE/ADDITION | 9 CONTROL SUPPLEMENT | XOTHER *(SPECIFY BELOW)* |
| 9 MEETING PLANNED BY | | |

II. BIOMETRICS

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| 9 TYPE A OR B NDA REVIEW | 9 CHEMISTRY REVIEW |
| 9 END OF PHASE II MEETING | 9 PHARMACOLOGY |
| 9 CONTROLLED STUDIES | 9 BIOPHARMACEUTICS |
| 9 PROTOCOL REVIEW | 9 OTHER |
| OTHER | |

III. BIOPHARMACEUTICS

| | |
|---|---|
| 9 DISSOLUTION | 9 DEFICIENCY LETTER RESPONSE |
| 9 BIOAVAILABILTY STUDIES | 9 PROTOCOL-BIOPHARMACEUTICS |
| 9 PHASE IV STUDIES | 9 IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

| | |
|---|---|
| 9 PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | 9 REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| 9 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | 9 SUMMARY OF ADVERSE EXPERIENCE |
| 9 CASE REPORTS OF SPECIFIC REACTIONS*(List below)* | |
| 9 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | 9 POISON RISK ANALYSIS |

V. SCIENTIFIC INVESTIGATIONS

| | |
|---|---|
| 9 CLINICAL | 9 PRECLINICAL |

COMMENTS/SPECIAL INSTRUCTIONS:

**TRADE NAME REVIEW**

Roche has submitted the name " — " as the trade name for their RIBAVIRIN/INTERFERON combination product for the treatment of hepatitis C virus infection. This name is submitted for the convenience package only, which will combine both components into a single packaging configuration. CBER will be the primary review for this name, as they are the primary review center for this combination application. For the ribavirin product, planned to be available under separate packaging, they have submitted the name "COPEGUS™." As a back up to "COPEGUS™", they submit the name " — ." Please evaluate Roche's choice of names for their NDA (Number unknown). Anticipated submission date for the combination BLA/NDA is June 7, 2002. A point of contact for the name review in CBER is Nancy Chamberlin, who may be reached at 7-6095. A point of contact for overall project management in CBER is Karen Winestock, who may be reached at 7-5369. Additionally, CBER has notified my that their preliminary plan is to reject the name "PEGASYS®, which will probably lead to the rejection of the the combination name, and if CDER agrees, the rejection of the name "COPEGUS™."

CC:

| | |
|---|---|
| SIGNATURE OF REQUESTER<br>Destry Sillivan | METHOD OF DELIVERY *(Check one)*<br>: MAIL 9 HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

**CONSULTATION RESPONSE**
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**
**OFFICE OF DRUG SAFETY**
**(DMETS; HFD-420)**

| DATE RECEIVED: 5/30/02 | DUE DATE: 8/13/02 | ODS CONSULT #: 02-0126 |
|---|---|---|

**TO:**

Debra Birnkrant, M.D.
Director, Division of Anti-Viral Drug Products
HFD-530

**THROUGH:**

Destry Sillivan
Project Manager, Division of Anti-Viral Drug Products
HFD-530

| **PRODUCT NAME:** | **NDA SPONSOR:** Hoffmann-La Roche, Inc. |
|---|---|
| Copegus (Ribavirin Tablets) 200 mg<br><br>NDA #: 21-511 (IND #: 58,827) | |

**SAFETY EVALUATOR:** Jennifer Fan, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Copegus" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:**
DMETS has no objection to the use of the proprietary name, "Copegus". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary/established names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**HFD-420; Rm. 15B32**
**Center for Drug Evaluation and Research**

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** July 31, 2002

**NDA NUMBER:** 21-511

**NAME OF DRUG:** Copegus (Ribavirin Tablets) 200 mg

**NDA HOLDER:** Hoffmann-La Roche, Inc

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530) for assessment of the tradename "Copegus", regarding potential name confusion with other proprietary/established drug names.

PRODUCT INFORMATION

"Copegus" is the proposed proprietary name for ribavirin tablets and is indicated in combination with peginterferon alfa-2a, recombinant injection for the treatment of chronic hepatitis C in patients with compensated liver disease. Ribavirin is a synthetic nucleoside analogue with antiviral activity. The daily dose of "Copegus" is 800 mg to 1200 mg administered orally in two divided doses. The recommended duration of treatment for patients untreated with ribavirin and interferon alfa-2a is 24 to 48 weeks. "Copegus" will be available as a 200 mg tablet and is supplied in bottles of 168, ) tablets.

CBER's Advertising and Promotional Labeling Branch has evaluated the proprietary names "Pegasys" and and has found the names unacceptable on May 15, 2002.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Copegus" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

[1] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

## A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Copegus". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel had sound-alike concerns with *Copaxone, Codituss,* and *Codotuss*. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

2. DDMAC had no concerns with *Copegus*.

Table 1

| Product Name | Dosage form(s); Generic name | Usual adult dose* | Other** |
|---|---|---|---|
| Copegus | Ribavirin (Rx)<br>Tablet: 200 mg | 800 mg to 1200 mg daily in two divided doses for 24 to 48 weeks | |
| Copaxone | Glatiramer Acetate (Rx)<br>Injection: 20 mg | 20 mg/day injected subcutaneously. | *SA |
| Codituss DH | Hydrocodone Bitartrate, Phenylephrine Hydrochloride, and Pyrilamine Maleate (Rx)<br>Syrup: 1.66 mg/5 mg/8.33 mg | 5 to 10 mL every 4 hours. | *SA |
| Codotuss | Guaifenesin and Hydrocodone Bitartrate (Rx)<br>Syrup: 100 mg/5 mg | 5 mL every 4 hours and at bedtime up to 30 mL per day . | *SA |

*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

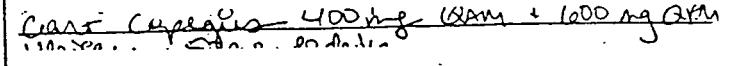
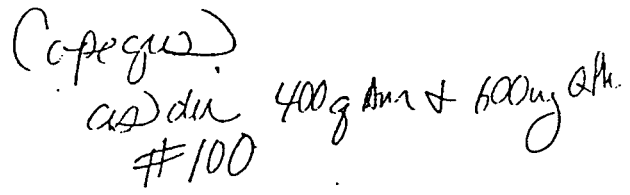


[4] WWW location http://www.uspto.gov.
[5] WWW location http://www.thomson-thomson.com.

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

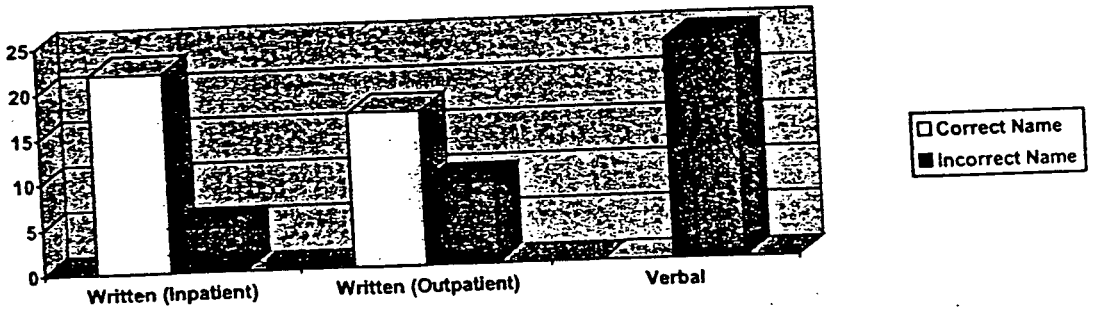
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Copegus" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Copegus" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTION |
|---|---|
| *Inpatient Rx:*  | *Outpatient Rx:* Copegus. Use as directed. 400 mg AM, 600 mg each PM. Dispense number 100. |
| *Outpatient Rx:*  | |

### 2. Results:

*Results of these exercises are summarized below:*

| Study | # of Participants | # of Responses (%) | Correctly Interpreted "Copegus" | Incorrectly Interpreted |
|---|---|---|---|---|
| Written Inpatient | 39 | 27 (69%) | 22 (81%) | 5 (19%) |
| Written Outpatient | 36 | 26 (72%) | 17 (65%) | 9 (35%) |
| Verbal Outpatient | 33 | 24 (73%) | 0 (0%) | 24 (100%) |
| Total | 108 | 77 (71%) | 39 (51%) | 38 (49%) |




Among the written inpatient prescriptions, 5 (19%) out of 27 respondents interpreted "Copegus" incorrectly. Such incorrect interpretations included *Copergus* (2 respondents, 7%), *Capegus* (1 respondent, 4%), and *Copegies* (1 respondent, 4%). One respondent could not interpret the name and, therefore, did not provide a guess.

Among the written outpatient prescriptions, 9 (35%) out of 26 respondents interpreted "Copegus" incorrectly. Such incorrect interpretations included *Capegus* (3 respondents, 12%), *Copequa* (1 respondent, 4%), *Copequo* (1 respondent, 4%), *Capegro* (1 respondent, 4%), *Copequod* (1 respondent, 4%), *Copegris* (1 respondent, 4%), and *Copequs* (1 respondent, 4%).

Among the verbal outpatient prescriptions, 24 (100%) out of 24 respondents interpreted "Copegus" incorrectly. Such incorrect interpretations included *Copagus* (13 respondents, 54%), *Copega* (3 respondents, 13%), *Copegas* (2 respondents, 8%), *Copagas* (2 respondents, 8%), *Copagis* (1 respondent, 4%), *Copagen* (1 respondent, 4%), *Kopagas* (1 respondent, 4%), and *Copegis* (1 respondent, 4%).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Copegus", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names include *Copaxone*, *Codituss*, and *Codotuss*.

*Copaxone* is the proprietary name for glatiramer acetate and is indicated for the reduction of the frequency of relapses in patients with RRMS (relapsing-remitting multiple sclerosis). The recommended dose of *Copaxone* is 20 mg a day injected subcutaneously. It is available as a 20 mg injection (single-dose 2 mL vial) that needs to be reconstituted with the diluent (sterile water for injection) supplied. *Copaxone* sounds similar to "Copegus" since both names begin with the "cop". However, the "axone" in *Copaxone* and "egus" in "Copegus" are very different. There is no overlap in dosage form, dosing directions, and total daily dose. These differences would decrease the potential risk in a medication error occurring between these two products.

*Codituss DH* is a distributor's proprietary name for an antitussive combination product containing hydrocodone bitartrate, phenylephrine hydrochloride, and pyrilamine maleate. It is available as an oral syrup. *Codituss* sounds similar to "Copegus"; however, *Codituss* also has a "DH" associated with its name, which may distinguish it from "Copegus". There is no overlap in dosage form (syrup vs. tablets) and dosing directions (5-10 mL or 1-2 teaspoonsful every 4 hours vs. 2-3 tablets twice a day). These differences would decrease the potential risk of a medication error occurring between these two drug products.

*Codotuss* is a distributor's proprietary name for an antitussive with expectorant combination product containing hydrocodone bitartrate and guaifenesin. It is also available as an oral syrup. *Codotuss* sounds similar to "Copegus". However, since there is no overlap in dosage form (syrup vs. tablet) and dosing directions (5 mL or 1 teaspoonful every 4 hours and at bedtime vs. 2-3 tablets twice a day), the potential risk of a medication error occurring between these two drug products would be low.

In addition, CBER conducted a preliminary evaluation of "Copegus". The proprietary names *Pacis, Coreg, Congess, Cope, Cophene-S,* and *Co-gesic* were mentioned as potential sound-alike and look-alike names to "Copegus". However, *Cophene-S, Congess* (*Jr.* and *Sr.*), and *Cope* are no longer sold in the U.S. market.

*Pacis* (equivalent to 120 mg semi-dry weight) is a lyophilized powder for suspension that is used for the treatment of carcinoma in situ of the urinary bladder. The recommended induction course is a single dose of 120 mg instilled into the bladder once weekly for 6 weeks. "Copegus" and *Pacis* do not sound or look alike due to the "co" beginning and "gus" ending of "Copegus". Also, the dosage form, dosing directions, dose, and strength do not overlap. These differences reduce the potential risk of a medication error occurring between "Copegus" and *Pacis*.

*Coreg* is the proprietary name for carvedilol and is indicated for essential hypertension and congestive heart failure. It is available as a 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablet. The recommended starting dose for hypertesion is 6.25 mg twice daily and 3.125 mg twice a day for congestive heart failure. "Copegus" and *Coreg* do not sound or look alike since "Copegus" contains 3 syllables while *Coreg* contains two. Also, the "reg" in *Coreg* and is quite different (sound and look alike) than "pegus" in "Copegus". Even though *Coreg* and "Copegus" have overlapping dosage form and regimen, they differ in strength and dose. These differences reduce the potential risk of a medication error occurring between "Copegus" and *Coreg*.

*Co-gesic* is the proprietary name for the combination drug product containing hydrocodone bitartrate (5 mg) and acetaminophen (500 mg). The average adult dose is 1or 2 tablets every 4 to 6 hours where the maximum dose is 8 tablets per day. "Copegus" and *Co-gesic* do not sound or look alike since the "gesic" in *Co-gesic* looks and sounds different from "pegus" in "Copegus". Even though "Copegus" and *Co-gesic* are available in tablet form, there is no overlap in strength, dose, and directions of use. These differences reduce the potential risk of a medication error occurring between "Copegus" and *Co-gesic*.

CBER also had concerns with "Copegus" and chemotherapy regimens that are abbreviated as COP (Cyclophosphamide, Vincristine, and Prednisone), COPE (Cyclophosphamide, Vincristine, Cisplatin, and Etoposide), and COPP (Cyclophosphamide, Vincristine, Procarbazine, and Prednisone). DMETS feels that even though all these abbreviations and "Copegus" have "cop" in common, the "gus" ending in "Copegus" would distinguish "Copegus" from the COP, COPE, and COPP.

CBER had also commented on the sponsor's use of the PEG stem in "Copegus". According to Dan Boring (of the USAN council and LNC), the PEG stem has not yet been approved as a USAN stem. However, according to the *USP Dictionary of USAN and International Drug Names* (2001 edition), PEG is used as a prefix for pegylated drug entities. Since the "peg" in "Copegus" is not used as a prefix, it would not mislead practioners to believe that "Copegus" is a pegylated drug entity.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL

Include the dosage form "tablets" in the established name.

B. CARTON LABELING [redacted]

C. PACKAGE INSERT

1. [redacted]

2. Under the Dose Modifications, [redacted] section, it states that "Copegus" should be reduced in certain situations to 600 mg per day where 200 mg is given in the morning and 400 mg is given in the evening. However, in the Dosage Administration section, DMETS recommends clarification of the statement " [redacted] ' so that it would be clear what the actual amount is per dose.

## C. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name "Copegus".

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

/S/

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Jennifer Fan
8/14/02 11:48:45 AM
PHARMACIST

Jerry Phillips
8/14/02 11:55:59 AM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

## RECORD OF INDUSTRY MEETING

**Meeting Date:** December 20, 2000 **Time:** 1:30 p.m.

**IND:** IND —

**Drug:** ribavirin (Ro 20-9963)

**Indication:** Treatment of Hepatitis C infection

**Sponsor:** Hoffmann-La Roche.

**Type of Meeting:** Pre-NDA - Chemistry, Manufacturing, and Controls (Meeting Type B)

**FDA Participants:**
**DAVDP:**
Debra Birnkrant, M.D., Acting Division Director, DAVDP
Steve Miller, Ph.D., Chemistry Team Leader, DAVDP
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, DAVDP
Rao Kambhampati, Ph.D., Chemistry Reviewer, DAVDP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, DAVDP
Jooran Kim, Pharm.D., Clinical Pharmacology Reviewer, DAVDP
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVDP
Destry Sillivan, M.S., Regulatory Project Manager, DAVDP

**External Constituents**
Barbara Kowal-Wilson, Program Director, Drug Regulatory Affairs
Rolf Schulte Oestrich, Director, Analytical Development, Chemical Process Development
Nanvit Shah, Distinguished Research Leader, Pharmaceutical Research and Development
Arnold Ramsland, Group Leader, Quality Management
Peter Hunold, Global Supply Leader, Supply Chain Management
Marlene Modi, Clinical Director, Clinical Pharmacology
Shangdong Zhan, Principle Scientist, Pharmaceutical and Analytical Research
Albert Pichieri, Principle Scientist Pharmaceutical Process/Technical Development
Richard Rucki, Principle Scientist, Quality Management
Hashim, Ahmed, Senior Principle Scientist, Pharmaceutical Research and Development

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**Background:**

This meeting was requested by Hoffman-La Roche, Inc.(HLR), to discuss the Chemistry, Manufacturing, and Controls (CMC) program for ribavirin, exploring the suitability of this program to support the NDA/BLA approval of PEGASYS and ribavirin combination therapy for the treatment of Hepatitis C infection.

DAVDP comments are shown in **BOLD** font, and the sponsor's comments/questions are shown in normal font.

**Discussion:**

1. Does the agency agree that it is sufficient to provide [redacted] of stability results for the registration batches of the API manufactured in [redacted] and [redacted] months of stability data for API manufactured in Hoffman-La Roche, Basel, Switzerland at the time of NDA filing?

   **DAVDP agrees that the proposed stability package is acceptable. However, DAVDP would be interested in the reasons for the differences between the two synthetic routes utilized by the Basel and [redacted] manufacturing facilities.**

   HLR clarified the reason for differences between the two synthetic routes utilized by the Basel and [redacted] manufacturing facilities, as follows:

   Basel uses [redacted] in the synthesis so the process can be accomplished at [redacted]. This is done for safety reasons.

2. Is the proposed protocol for the comparison of the physio-chemical characterization of the second source of API from Hoffmann- La Roche, Basel, Switzerland to the [redacted] API sufficient to establish the equivalence of the two API's? Additionally, does the FDA concur that a bioequivalence study is not needed to qualify the use of the second source?

   **DAVDP recommends that a minimum of [redacted] batches be produced at each site to establish equivalence of the API. Additionally, it is recommended that release data from a minimum of [redacted] batch of drug product manufactured with the Basel API be included in the application.**

   **DAVDP agrees that a bioequivalence study is not needed to qualify the use of the second source.**

3. Is the previously agreed upon bracketing approach for the drug product manufactured at Hoffmann-La Roche, Nutley, New Jersey sufficient, regardless if the second source of tablet manufacture at [redacted] is included in the original NDA or not? Is this bracketing approach sufficient to support post approval change to provide for [redacted] as an alternate drug product manufacturer, if Patheon is not included in the original NDA?

   **It is unlikely that data from drug product manufactured at [redacted] will be available during the review cycle. DAVDP recommends that HLR discuss this issue with us in the future, prior to filing stability data for tablets manufactured at [redacted] should the situation change.**

   **HLR and DAVDP agree that statistical analysis of stability data from the Nutley drug product will be submitted approximately one month after filing.**

   Additionally, an expiration dating period of 36 months is proposed.

   **An expiration dating period of 36 months would be in excess of what would normally be considered as the maximum expiration dating period for stable drug product (real time data on the primary batches plus six months).**

HLR indicated that a significant amount of supportive stability data is available.

**DAVDP requests that a summary of these data (number of batches, available timepoints, formulations and packaging configurations) be submitted prior to filing. This will allow DAVDP and HLR to reach agreement on the role of these batches in determining the expiration dating period.**

**DAVDP agrees that the bracketing approach agreed to previously for the stability data on Nutley drug product can also support as an alternate drug manufacturer regardless of whether the stability data is provided in the NDA or as a post-approval change.**

4. Has the been sufficiently characterized and controlled in the starting material? And does the Agency agree that testing of optical purity is not necessary in the ribavirin tablets.

**DAVDP agrees that the has been sufficiently characterized. However, DAVDP recommends that HLR include a commitment to reconfirm the enantiomeric purity of the starting material as a one time study during the qualification of new starting material suppliers.**

**DAVDP agrees that testing of optical purity does not need to be included in the ribavirin tablet specification. For acceptance testing of outsourced API, DAVDP recommends, at a minimum, that a be performed.**

**HLR indicated that full testing is carried out on outsourced API, which DAVDP agrees is preferable.**

5. Does the Agency agree that the polymorphic forms of the API are sufficiently characterized, and that an appropriate limit test is sufficient to ensure the respective quality of the ribavirin tablets?

**DAVDP agrees that HLR has adequately characterized the two polymorphic forms of ribavirin.**

**DAVDP recommends that at a minimum a test be included in the drug substance specification. However, would also be acceptable.**

6. Is a single point dissolution test sufficient for the release of the ribavirin tablets?

**DAVDP agrees that a single point dissolution test is acceptable.**

**Additional Discussion Topics:**

1. **HLR will likely need to supply patient information in every unit of package for the count bottle. HLR should consider how such information would be provided. Please consult 21 CFR Part 208, "MEDICATION GUIDES FOR PRESCRIPTION DRUG PRODUCTS" for further guidance pertaining to this issue.**

HLR will research this issue and reply at a later date