

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 103949/5002

Administrative/Correspondence Reviews

MEMORANDUM

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

DATE: August 7, 2001
FROM: Victoria Tyson-Medlock
TO: License Number 0994
SUBJECT: Schering Summary Basis of Approval
BLs: 103949/5002
Manufacturer: Schering Corporation
2100 Galloping Hill Road
Kenilworth, NJ

- **Drug License Name:** Peginterferon alfa-2b and Ribavirin
- **Drug Trade Name:** PEG-Intron and Rebetol
- **Indications and Usage**
Peginterferon alfa-2b in combination with Ribavirin is indicated for the treatment of chronic hepatitis C in patients not previously treated with interferon alfa who have compensated liver disease and are at least 18 years of age.
- **Dosage Form, Route of Administration and Recommended Dosage**
- Peginterferon alfa-2b is supplied in a lyophilized powder in a single-use vial containing 50 µg/ 0.5 mL, 80 µg/0.5 mL, 120 µg/0.5 mL and 150 µg/ 0.5mL vials, with a 5-mL vial of PEG-Intron diluent (Sterile Water for Injection), two disposable 1-mL (Becton-Dickenson Safety-Lok) ½ inch-27 gauge syringes with needles and needle guards, and alcohol swabs. Peg-Intron is administered subcutaneously at a dose of 1 Tg/kg once a week for 48 weeks. There are no preservatives.
- **Ribavirin (REBETOL)**
REBETOL is supplied in 200 mg capsules for use in combination with Peginterferon alfa-2b at a dose of 800 mg per day.

Basis of Approval

The basis of approval of Peginterferon alfa-2b in combination with Ribavirin for the treatment of chronic hepatitis C is contained in the following appended documentation:

Review Discipline	Reviewer	Date	Location
Clinical	Louis Marzella	9-19-01	CBER Correspondence
Pharm/Tox	Anne Pilaro	8-10-01	CBER Correspondence
Biostatistics	Jawahar Tiwari	8-3-01	CBER Correspondence
Product consult	Ralph Bernstein and Edward Max	7-26-01	CBER Correspondence
Clin/Pharm consult	Jooran Kim	8-6-01	CBER Correspondence

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Telecon Record

Date: August 7, 2001
Time: 3:30 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner to discuss the following issues:

- ◆ the vial and carton labels submitted for PEG-Intron are acceptable and should be submitted in hard copy.
- ◆ submit a request to withdraw the convenience package labeling.
- ◆ submit a formal, signed letter outlining the post marketing commitments.
- ◆ to make sure that REBETOL is capitalized throughout the PI and Medication Guide.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



Telecon Record

Date: August 6, 2001

Time: 3:00 P.M.

CBER Personnel: Louis Marzella
Sharon Risso
Anne Pilaro
Jay Siegel
Victoria Tyson-Medlock
Glen Jones

Company Personnel: Rachael Steiner
Penny Giles
Ken Koury
Jan Albrecht
Mei-Hsiu Ling
Marielle Cohard
Carol Marrow
Clifford Brass
Mark Laughlin
Joe Lamendola

INTRODUCTION

This teleconference was held to discuss the specifics of the post marketing studies that will be required to optimize the PEG-Intron and Rebetol dose, dosing regimen and the duration of treatment.

Weight-Based Dosing of Rebetol

The agency informed the sponsor that weight-based dosing of Rebetol is not acceptable and further studies would be required to determine if weight-based dosing is superior to fixed dosing. If weight-based dosing is superior to fixed dosing a supplement would have to be submitted to revise the package insert. Dr. Siegel advised the sponsor to commit to safer ways

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to give this therapy. The agency raised concern regarding the dose-dependent toxicities and serious

adverse events associated with Rebetol. Specifically, in the study submitted to support the PEG-Intron and Rebetol combination therapy 57% of the patients treated with ≥ 13 mg/kg of Rebetol required dose modifications and 15% discontinued treatment because of adverse events that included anemia and leukopenia.

The agency is not comfortable with the analysis that was done to support weight-based dosing, and informed the sponsor that these analyses were inappropriate and lead to misleading false claims. The sponsor objected to the use of inappropriate analysis. Dr. Siegel state that dangerous conclusions were made and that sketchy data was over interpreted.

A sponsor investigator trial is underway evaluating fixed versus weight-based dosing of Rebetol in combination with 1.5 μ g/kg PEG-Intron dose.

Duration of Treatment

The agency informed the sponsor that further exploration of the duration of treatment with PEG-Intron and Rebetol would be required. The agency stated that certain subsets of patients (genotypes 2 and 3; genotype 1 with low viral titers) six months of treatment might be just as effective as 12 months. The agency advised the sponsor to revise the European study or conduct another study to evaluate the duration of treatment. This study should include a sample size of 1500 patients with two arms (6 and 12-months treatment) and should be powered to detect a 7% difference in response. If warranted, a prior approval supplement would have to be submitted to include a shorter duration of treatment in the package insert.

Optimization of the PEG-Intron Dose

The agency stated that dose optimization should have been explored in Phase 2 studies. The sponsor's hypothesis regarding the superiority of the 1.5 μ g PEG-Intron dose compared to the 1.0 g/kg dose were not supported by the data and the PEG-Intron dose must be optimized. A post marketing study would be required comparing the 1.0 and 1.5 μ g dose of PEG-Intron in 1500 patients. The sponsor asked why 750 patients per arm would be required for this study. The agency informed the sponsor that the standard of evidence is different for an approved drug. This product has public health issues that must be addressed regarding the dose and duration of treatment. The agency suggested revising the ongoing study by increasing the sample size, particularly the international study. A prior approval supplement would have to be submitted to include this information in the package insert. The timelines for submission of the supplement will be agreed upon in advance.

A sponsor investigator trial is underway evaluating fixed versus weight based dosing of Rebetol in combination with 1.5 µg/kg PEG-Intron dose.

The sponsor will use the 24-week data if predictive to choose the Rebetol dose for the PEG-Intron optimization study. The sponsor agreed to evaluate the 1.0 versus 1.5 µg/kg doses in combination with Rebetol. The sponsor will evaluate the six months interim data to identify the Rebetol dose and duration of treatment. The agency advised the sponsor to submit two protocols to the IRB for review (one with fixed dosing, the other with weight-based dosing) so that they can proceed without delay when the agency agrees to the study design. This study will be initiated in June 2002, and completed by December 2003.

Dr. Siegel asked the sponsor to submit an analysis that justifies the use of in-treatment data to predict sustained response to treatment. If that analysis does not support the use of in-treatment data, the sponsor should initiate enrollment for this study in November 2001 using fixed-dose Rebetol. A protocol amendment would be required. Dr. Siegel informed the sponsor that a large trial would be required about 1,200 patients to detect a small percent change.

Dr. Marzella asked the sponsor how they would integrate the duration of treatment study with other studies. The sponsor will conduct a six-month study with genotypes 2 and 3. Dr. Siegel stated that the outcome would be uncertain because it is uncontrolled. The sponsor was referred to the agency's ICH-E10 document.

Additional studies will be required to better characterize the food effect of Rebetol.

The results of a carcinogenesis study of Rebetol will be submitted to CDER.

Ophthalmologic will be required at baseline to determine which patients have retinopathy.

The sponsor was asked to collapse fatigue and asthenia in the adverse events table in the package insert.

The sponsor was asked to submit timelines for the Phase 4 commitments.

On August 3, 2001 I sent by e-mail and fax a copy of the final draft of the Medication Guide for PEG-Intron and Ribavirin to Schering.

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✓ § 552(b)(5) Draft Labeling

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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



Telecon Record

Date: August 2, 2001
Time: 2:00 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner at Schering and asked that they submit the press release for the PEG-Intron and Ribavirin combination. She stated that it has not been written as yet but they will submit it as soon as possible.

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TELECON MINUTES

Telecon Date: August 2, 2001

Participants

FDA: Sue-Chih Lee, Ph.D., CDER/OCPB/DPE3
Jooran Kim, Pharm.D., CDER/OCPB/DPE3
Russell D. Fleischer, M.D., CDER/DAVDP
Libero Marzella, M.D., CBER

Schering-Plough: Jan Albrecht, Ken Koury, Mei-Hsiu Ling, Frank Jen,
Gerry Hajian, Penelope Giles, Mark Laughlin, Joe
Lamendola, Rachael Steiner

Re: FDA Comments on PK/PD Analysis of Ribavirin

This telecon was held to clarify CDER's comments on the PK/PD analysis of ribavirin, which was conveyed to the sponsor through CBER during a telecon between CBER and the sponsor on August 1, 2001. The discussions follow each comment below:

1. Regarding the population PK (PPK) analysis:

FDA Comment 1-a:

The ribavirin concentration-time profile at steady state was assumed to be flat. The sponsor did not discuss the error associated with this assumption. This error may be assessed through simulations using Phase I/II data.

Dr. Lee stressed that there was no information in the submission about the error associated with the "flat-profile" assumption. The sponsor indicated that simulation was previously performed to assess this error. Dr. Lee requested that this information be submitted for our review.

FDA Comment 1-b:

It appears that total body weight was used in the calculations of creatinine clearance. The sponsor should revise the calculations by using the ideal body weight instead. Additionally, it is noted that at least 25% of the patients had serum creatinine below 0.8 mg/dL. Please explain or correct as appropriate.

Dr. Lee explained that preferably each covariate in the analysis represents a unique factor. Creatinine clearance should be calculated based on ideal body weight instead of total body weight to reflect patients' renal function. The sponsor agreed to recalculate creatinine clearance and redo the PPK analysis. Dr. Lee also indicated that some patients had low serum creatinine with the lowest being less than 0.4 mg/dL. The sponsor

indicated that these patients were relatively healthy and agreed to check the serum creatinine data.

FDA Comment 1-c:

The PPK model has an implicit assumption of dose proportionality. This assumption may hold for doses up to 1200 mg/day based on previous studies but the 800 mg/day dose has not been studied. The sponsor should provide information that confirms dose proportionality up to the highest recommended dose (800 mg/day).

Dr. Lee asked whether 800 mg/day means 400 mg BID. The sponsor indicated that it would be [800 mg doses because the dosage form comes in 200-mg units. The sponsor also indicated that they had studied PK at 800-mg dose level. Dr. Lee requested to see the report. (In a separate conversation on the same day, Dr. Giles stated that the 800-mg PK study was most likely a single dose study. Dr. Lee indicated that this drug has a very long half-life and accumulates upon multiple dosing. Therefore, the single dose study may give some indication about the absorption but not answer the question about linearity.)

(She would also check to see whether there was steady state dose proportionality data for doses up to 1200 mg/day.)

FDA Comment 1-d:

The sponsor allowed separate estimates of covariate "coefficients" for male and female subjects in the PPK analysis. This reviewer has reanalyzed the data by treating gender as one covariate and keeping coefficients for all other covariates the same for both genders. We recommend the latter method be used unless there are reasons to do otherwise.

The sponsor explained that they analyzed data the way they did to minimize intersubject variabilities. Dr. Lee inquired about how much decrease in variabilities was seen in their analyses. The sponsor responded that the reduction was small and agreed to reanalyze using the method we recommended.

FDA Comment 1-e:

Although weight appears to be a statistically significant factor for exposure (or C_{ss}), the sponsor did not provide information on how incorporating weight into the model changes the variabilities. (Based on this reviewer's analysis, the reduction in variabilities is low. Therefore, weight does not lend itself as an apparent factor for dose adjustment. Further examination on how the dose adjustment translates into better risk/benefit ratio is needed. In this regard, the sponsor did perform PD analyses for both efficacy and safety.)

The sponsor did not have any question with respect to this comment.

FDA Comment #2

Regarding the PD analyses: The sponsor compared the safety and efficacy of the proposed weight-based dosing regimen to those of the clinical trial dose (800 mg/day).

This assessment was conducted lumping all patients together. The sponsor should conduct simulations to evaluate the impact on safety and efficacy for each weight range specified in the weight-based dosing recommendation. This simulation should take into account the PK and PD variabilities/distributions.

First of all, the sponsor indicated that their weight-based dosing recommendation was proposed primarily based on statistical analyses of clinical safety and efficacy data. The PK/PD analyses were performed to support this proposal. Since Dr. Lee did not review this part of the analyses, **Dr. Marzella responded to this statement**

The sponsor then asked for clarification on what weight ranges should be used for simulation. Dr. Lee replied that the weight ranges intended for weight-based dosing in clinical settings should be used for simulation.

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Telecon Record

Date: August 1, 2001

Time: 3:00 p.m.

CBER Personnel: Victoria Tyson-Medlock
Louis Marzella
Martin Green

Company Personnel: Rachael Steiner
Jan Albrecht
Ken Koury
Mei-Hsiu Ling
Marielle Cohard
Carol Morrow
Penny Giles
Clifford Brass
Mark Laughlin
Joe Lamendola

This teleconference was held to discuss the Phase 4 commitments for the PEG-Intron and Ribavirin supplement.



Telecon Record

Date: August 1, 2001
Time: 4:30 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner and sent her an e-mail and fax of the final draft of the PEG-Intron and Ribavirin package insert.

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_____ § 552(b)(5) Draft Labeling

17 July 01 Telecon 12:30 pm

Participants:

Ralph M. Bernstein for CBER

☐

☑

CBER initiated the call.

CBER requested figure legends annotating the data — provided, which ostensibly validates the — HCV RT PCR. CBER also requested the SOPs frequently referred to (but not provided) thru out the — documents. CBER requested a clarification of several — specific terms, as well as requesting the methods validation for the — assay. — agreed to provide the data in an expeditious manner.

The Telecon was concluded.

RM Bernstein, PhD
Staff Fellow
Lab of Gene Regulation,
Department of Therapeutic Proteins
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
The Food and Drug Administration
29 Lincoln Drive
Building 29A, Room 2B09
Bethesda Maryland 20892

TELECON MINUTES

Telecon Date: July 10, 2001

Participants

FDA: Sue-Chih Lee
Clinical Pharmacology and Biopharmaceutics Reviewer

Schering-Plough: Penelope Giles, Paul Glue, and J. Frank Jen

Re: PK/PD Analysis of Ribavirin
Submitted in support of BLA 99-1488

This reviewer had two questions for the sponsor. These questions were conveyed to the sponsor on July 9, 2001 by Dr. Lou Marzella, Medical Officer in CBER. This reviewer was then informed by Dr. Marzella that the sponsor would like to have a telecon to clarify the questions. Therefore, this reviewer called the sponsor on July 10, 2001. The questions and the sponsor responses are listed below.

FDA Q #1:

In the data set used for PK/PD analyses (including population PK, and safety and efficacy data), are there imputed data? If so, please indicate which data were imputed and how the imputation was performed.

Sponsor's response:

All data used in the analyses were actual data obtained in clinical trials. There were no imputed data.

FDA Q #2:

Dose reduction for ribavirin occurred during the trial (C/I 98-580). Please provide a table showing the dose reduction event(s) and the time it occurred for individual patients.

Sponsor's response:

The sponsor asked to clarify this question. This reviewer indicated that since dose reduction did occur during the trial, the dose used for PK/PD analysis might not be the actual dose received by the patients. The sponsor responded that actual dose was used in the population PK analysis but nominal dose was used in toxicity data because few patients had a dose reduction before Week 4 when the toxicity was assessed. The sponsor will provide the following:

- a. An article that they recently published (Therapeutic Drug Monitoring, 22:555 (2000)) which would help clarify my question.

- b. Dose reduction information for individual patients. This will include Patient ID, initial dose, revised dose, and the time when dose reduction occurred.

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July 17, 2001

Firm: Schering -Plough (Brinny) Co.
Innishannon
County Cork, Ireland
U.S. License #0994-001
CFN #9616653

STN #103949/5002; is for the Schering PEG-Intron and Ribavirin.

There are no ongoing or pending investigations or compliance actions with respect to the above facility or its product(s).

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12 July 01

Telecon with —
Representing CBER Ralph M Bernstein
Representing L J

CBER initiated the call

Responding to several voice messages from — CBER contacted —
and

discussed the regulatory data — is compiling and sending to CBER
for review (validation data for — HCV RT PCR). — had requested
a Telecon with CBER for Thursday morning (12 July 01) and asked that
the Telecon could include CBER, L J and L

J CBER suggested that a Telecon would be more appropriate
when CBER has received the initial data from — so that CBER could
more adequately address any deficiencies. CBER agreed to contact —
once the — data arrives at CBER and when CBER has completed a
basic examination of the data.

The Telecon was concluded.

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Telecon Record

Date: July 2, 2001
Time: 11:00 a.m.
CBER Personnel: Victoria Tyson-Medlock
Jooran Kim
Company Personnel: Rachael Steiner

Dr. Jooran Kim and I called Schering and requested the text portion of the summary of study report 580; population pk/pd analysis in study report 580.

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Three telecons were held today with Schering and /or — in respect to Schering's BLS for /product/.

Telecon 1

5 July 01, Midmorning

Amy Rosenberg and Ralph Bernstein for CBER
and Rachel Steiner for Schering.

CBER initiated the call.

The quantitative RT PCR for HCV was discussed, including the lack of information being provided by — to Schering. CBER requested that the information related to the assay's specificity, sensitivity, robustness and reproducibility be included as a supplement to the BLS. Schering suggested that they would contact — and respond to CBER quickly. The telecon was concluded.

Telecon 2

5 July 01, approximately 4 pm.

Amy Rosenberg and Ralph Bernstein for CBER

‡ Penny /surname/ for Schering

CBER initiated the call.

— Schering and CBER discussed the data and validation that CBER requires for a thorough review of the — quantitative HCV RT PCR. — offered to send data detailing the specificity, sensitivity, robustness and reproducibility of the assay, and that — would and could contact CBER (Ralph Bernstein) directly for further assistance in compiling the requested data. The telecon was concluded

Telecon 3

5 July 01, 5:10-5:30 pm.

Ralph Bernstein for CBER

Ken /surname/ for —

NGI initiated the call.

— and CBER further discussed the data necessary for CBER to adequately review the — HCV RT PCR. — said that they would Fed Ex the submission directly to CBER as soon as it is compiled. CBER reminded — to include the assay validation in its entirety (from serum preparation, to PCR amplification, to Southern Blotting), but

that representative examples would be adequate (i.e. — does not have to send CBER hundreds of gels).

The call was concluded.

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Telecon Record

Date: June 29, 2001

Time: 11:00 a.m.

CBER Personnel: William Schwieterman
Louis Marzella
Jawahar Tiwari
Victoria Tyson-Medlock

Company Personnel: Rachael Steiner
Penny Giles
J.J. Garaud
Jan Albrecht
Mei-Hsiu Ling
Marielle Cohard
Michael Geffner
Carol Marrow
Clifford Brass

INTRODUCTION

This teleconference was held to inform the sponsor of certain issues that have come up in the review of this biologics license supplement for the treatment of chronic hepatitis C, and to discuss a draft protocol submitted at the agencies request to evaluate the safety and efficacy of the 1.0 versus the 1.5 $\mu\text{g}/\text{kg}$ dose of PEG-Intron in combination with weight-based dosing of ribavirin.

DISCUSSION

The agency informed the sponsor that there is not enough data to support the weight-based dosing claim of ribavirin.

The sponsor was informed that based on the regulations they cannot charge patients for the Peg-Intron and ribavirin combination therapy. The sponsor can apply for cost recovery.

The 1.0 versus 1.5 $\mu\text{g}/\text{kg}$ Peg-Intron dose protocol was discussed internally and the agency made the following recommendations:

- To increase the number of patients proposed for this trial to at least 2, 000 to 5, 000 patients. To conduct an equivalent study to reject the 95 % confidence interval, 4 % absolute difference from the control. The agency suggested including a 1.5 $\mu\text{g}/\text{kg}$ PEG-Intron in combination with 800 mg ribavirin as a control arm.
- The Dr. L trial can support labeling changes if adequately designed.
- To focus on the safety and efficacy of the combination therapy since it is likely to be the standard of care and include adequate monitoring and collection of serious adverse events. This issue is a major concern regarding the risk-benefit of this therapy because of the toxicities associated with these agents and for the first 10 or 20 years of the CHC infection patients do well without therapy. The agency also raised the concern that millions of patients will be receive this therapy and a lot of patients have very poor outcomes.
- Further dose exploration/optimizations would be required. The agency also raised concerns about the interaction between ribavirin and PEG-Intron.
- Enriching the study with genotype 1 patients.

The agency asked the sponsor to submit a protocol as soon as possible because the PDUFA deadline is August 7, 2001. Schering stated that they would submit a proposal next week.



Telecon Record

Date: June 12, 2001
Time: 9:30 a.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Penny Giles

I called Schering and asked Dr. Penny Giles to submit a copy of the Rebetrone package insert in WORD and PDF format so that it can be loaded onto the EDR. The Rebetrone package insert will help to review the PEG-Rebetrone labeling.

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Telecon Record

Date: June 1, 2001

Time: 1:30 p.m.

CBER Personnel: Victoria Tyson-Medlock
Jooran Kim

Company Personnel: Rachael Steiner

Dr. Jooran Kim and I called Schering and informed Rachael Steiner that the electronic study reports C/198-580, and C 1 requested on May 3, 2001, are not useable. We asked the sponsor to submit the electronic output listings for these population pharmacokinetic/pharmacodynamic studies. Dr. Kim explained that they need the electronic summary reports for C 1 Ms. Steiner stated that she would submit them as soon as possible.

6 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



Telecon Record

Date: May 31, 2001
Time: 4:30 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

Schering called and asked if they could charge for the PEG-Intron and Ribavirin that will be administered in a study that the agency requested to compare the 1.0 versus 1.5 mcg/kg PEG-Intron dose with Ribavirin. I informed the sponsor that they would have to submit a request to charge for this therapy and to contact Bette Goldman for more information.

I asked Ms. Steiner to submit a copy of Volume 1 of the PEG-Intron and Ribavirin supplement to Mr. Destry Sullivan in CDER.

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Telecon Record

Date: May 23, 2001
Time: 12:00 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

- I called Schering at the request of Dr. Ralph Bernstein and left a message asking them to provide a time line for submitting the specifics of — , quantitative assay. I also asked the sponsor to submit the protocol and data supporting the protocol for the genotyping assay used by Schering.

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Telecon Record

Date: May 21, 2001

Time: 2:00 pm

CBER Personnel: Ralph Bernstein
Victoria Tyson-Medlock

Company Personnel: Rachael Steiner

I called Schering with Dr. Bernstein to request information on — quantitative HVC-RNA PCR assay [] that was used to determine the number of copies/mL of HCV-RNA to support the primary endpoint. Ms. Steiner referred to the cross reference letter submitted to IND — for the qualitative assay, [] that are under review in ORBB. Dr. Bernstein explained that although this assay is used first for the presence of HCV-RNA the quantitative assay is a different assay. We also stressed the importance of submitting this information as soon as possible and originally requested this information on May 1, 2001. Ms. Steiner stated she will discuss this issue with their legal consultants and — and submit the information requested as soon as possible.

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TysonMedlock, Victoria

From: Schwieterman, william
Sent: Wednesday, May 16, 2001 9:18 AM
To: TysonMedlock, Victoria
Subject: FW: PEG & Riba BLs

Vicky:

Please add Ms. Janet Gress to the review team for BLA 103949/5002. Tx.

Bill

-----Original Message-----

From: TysonMedlock, Victoria
Sent: Tuesday, May 15, 2001 3:50 PM
To: Schwieterman, william
Cc: Gress, Janet
Subject: PEG & Riba BLs

Hi Bill,

please send me a memo adding Janet to the review team for 103949/5002. thanks

Hi Janet,

I called Schering and asked them to submit another set of CDs for this supplement. thanks

Vicky

TysonMedlock, Victoria

From: Dye, Earl
Sent: Tuesday, May 08, 2001 4:06 PM
To: TysonMedlock, Victoria
Cc: Hu, REN QUI; Rosenberg, Amy
Subject: STN 103949/5002

Vicki

Please add Ren Qui to the committee reviewing Scherings supplement for use of combination therapy with Peg-Intron and Ribavirin for Hep C. Ren Qui will assist in the review of the labeling. Thanks, Earl

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

DATE: May 3, 2001

FROM: Victoria Tyson-Medlock
Consumer Safety Officer
OTRR/DARP/AAB

SUBJECT: Mid-Cycle Meeting
Schering-Biologics License Supplement
PEG-Intron and Ribavirin
12:30-2:30
WOC I Room 200S

TO: BLs 103949/5002

◆ **Overview:**

Schering Corporation submitted a supplement to the PEG-Intron license to treat chronic hepatitis C (HCH) with a combination of 1.5 µg/kg of PEG-Intron once a week, by subcutaneous injection and > 10.6 mg/kg/day of Rebetol. This supplement was received on February 5, 2001, and assigned STN 103949/5002. The first action due date is August 7, 2001. This mid-cycle meeting was held to discuss the status of the review of this supplement.

◆ **Review Committee:**

Louis Marzella-Clinical Reviewer- Chairman
Ralph Bernstein-Product Consult Reviewer
Patricia Hasemann-Bioresearch Monitoring Reviewer
Jooran Kim-Clinical Pharmacology Consult Reviewer
Anne Pilaro-Pharmacology/Toxicology Reviewer
Jawahar Tiwari-Statistical Reviewer
Victoria Tyson-Medlock-Regulatory Coordinator

◆ **Milestones:**

Application Received-February 5, 2001
Committee Assignment-February 19, 2001-Assigned February 5, 2001
First Committee Meeting-February 26, 2001-Held February 21, 2001
Filing Meeting-March 22, 2001-Held on March 19, 2001
Filing Action-April 6, 2001-Letter Issued April 5, 2001
First Action Due Date-August 7, 2001

◆ **Future scheduled meetings:**

Labeling meetings will be scheduled to start after the Mid Cycle meeting. Schering submitted an amendment to this supplement on April 12, 2001, to provide the combination in a patient convenience package. This amendment contains container and package labels, a Medication Guide, a package insert and a request for review of the proposed trade name for the combination, PEG-REBETRON.

◆ **Status of Bioresearch Monitoring Inspection**

Patricia Hasemann could not attend this meeting but provided the following comments and asked to be made aware of any sites that the clinical reviewer feels should be inspected.

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◆ **Status of Product Consult Review**

Dr. Bernstein informed the team that [redacted] PCR assay, [redacted] is under review in the Office of Blood Research and Review [redacted]. The first action due date for this application is August 18, 2001. The review team asked Schering to submit specifics of [redacted] PCR assay.

◆ **Status of Pharmacology/Toxicology reviews**

Preclinical effects of combination PEG-Intron and ribavirin included severe anemia, neutropenia, thrombocytopenia, and deaths in monkeys treated with PEG-Intron and ribavirin at doses of 50 or 75 mg/kg/day. The hematologic effects observed pre-clinically with the PEG-Intron and ribavirin combination are similar to the effects observed with PEG-Intron alone; however, deaths were not observed in previous studies of PEG-Intron alone at similar doses to that used in the combination study.

The doses of PEG-Intron given in the toxicology studies were approximately 300 fold higher than the doses administered clinically. The deaths observed in the toxicology studies of the combination of PEG-Intron and ribavirin were considered related to the hematology effects and subsequent sepsis; cultures of peripheral blood, peritoneal fluid and pericardial fluid were positive for *Staphylococcus aureus* and *Streptococcus bovis*. Other findings included histologic evidence of bacterial colonies in the heart (accompanied by endocarditis), skin, muscle, and peritoneal tissue. In a second toxicity study using a range of doses of PEG-Intron and a fixed ribavirin dose, there were no monkey deaths, and no apparent adverse effects of the combination treatment on neutrophil anti-bacterial, phagocytic, and chemotactic functions.

◆ **Status of Clinical Pharmacology Consult reviews**

The weight-based dosing regimen proposed has not been studied. The sponsor has no experience with the — mg ribavirin dose and submitted modeled data in support of the weight-based dosing claim. There is a linear dose relationship with ribavirin doses between 800 and 1000 mg but not with doses between 1000 and — mg. The review team will contact the sponsor and request electronic clinical study reports for protocols C and C/198-580.

◆ **Status of Clinical review**

Currently the standard of treatment for HCV is Rebetron, Intron A and Ribavirin. If the combination therapy is approved it will become the new standard of treatment.

The Phase 3 randomized active-controlled, open-label study of 1580 patients with chronic HCV contained the following three treatment groups: 1) Peginterferon 1.5 µg/kg once weekly SC plus ribavirin 800 mg PO daily, 2) Peginterferon 0.5µg/kg once weekly SC plus ribavirin 1000/2000 mg PO daily, 3) interferon 3x10⁶ U SC TIW plus ribavirin 1000/1200 mg PO daily. Patients were treated for 12 months and followed for 6 months. The response to treatment (loss of HCV RNA at 6 months post-treatment) was 46% in the IFN/R and PEG 0.5/R groups and 52% in the PEG1.5/R group. The principal secondary endpoint (normalization of ALT) showed similar efficacy results. The liver biopsies showed minor decreases in inflammation and minimal decreases in fibrosis from baseline. The decreases were similar in the three groups.

Further dose exploration and optimization of PEG-Intron and Rebetol will be required pre-market or as a part of Phase 4 commitments. PEG-Intron monotherapy was approved at 1.0 µg/kg but the sponsor does not have experience with the 1.0 µg/ kg PEG-Intron dose in combination with Rebetol or the 1400 mg ribavirin dose. The agency is reviewing a proposal to compare the 1.0 and

1.5 µg/kg PEG-Intron doses in combination with weight-based ribavirin of dosing.

A teleconference was held on April 6, 2001, to discuss the weight-based dosing claim. During this teleconference the agency asked the sponsor to submit regression curves with different cut off points for the ribavirin dose.

Poor prognostic factors for HCH include age, gender, race, liver fibrosis, genotype and baseline viral load ($> 2 \times 10^6$ copies/mL). African Americans and Hispanics respond poorly to interferon therapy and Asiatic respond better.

The following additional analyses will be performed by the review team: analyses, including multivariate analyses, of body weight. vs. gender vs. size vs. dose of ribavirin; analyses of race and genotype, and viral load and genotype on treatment response.

The safety database for PEG-Intron was discussed. There have been two deaths and three attempted suicides that were related to depression. The agency stated adverse events appear to be more severe with the PEG-Intron and ribavirin combination. These adverse events include psychiatric events (75%), hallucinations, cognitive impairment, optic neuritis, bone marrow toxicities, fever, rigors, abdominal pain and application site reactions that include necrosis.

The following additional analyses will be performed; reporting frequency of adverse events in the U.S. versus Europe, safety data as a function of ribavirin dose/body weight.

◆ **Discussion of need for Advisory Committee**

The review team will decide whether this supplement should be presented at and advisory committee.

◆ **Discussion of need for Post-Marketing Commitments**

This issue will be discussed at a later date.

◆ **Action Items**

The review team will contact Schering to discuss the need for additional studies pre or post marketing that address the following:

- ◆ the lack of dose exploration and optimization of PEG-Intron and Rebetol;
- ◆ the proposal to conduct a study comparing the 1.0 and 1.5 µg/kg PEG-Intron dose in combination with weight-based dosing of Rebetol;
- ◆ the dose relationship and weight-based dosing of ribavirin;

- ◆ differences in the response based on gender and race; and toxicities

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Telecon Record

Date: May 3, 2001
Time: 3:00 P.M.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner at Dr. Jooran Kim's requests and asked that they submit electronic study reports for the following studies:

- ☐ Study C/197-010; and
- ☐ Study C/198-580

She will send a copy of these studies out on Monday.



Telecon Record

Date: May 1, 2001

Time: 10:00 am

CBER Personnel: Victoria Tyson-Medlock
Ralph Bernstein

Company Personnel: Penny Giles
Rachael Steiner

Dr. Ralph Bernstein and I called Schering and asked that they submit the most up to date information on C₁ PCR assay.

Dr. Bernstein informed the sponsor that the assay is not quantitative and inadequately documented. He asked the sponsor to submit information on the procedures for southern blotting, recovery of serum, validation of controls and quantitation of the assay. Dr. Giles said that she will look into it and submit the information requested.

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Telecon Record

Date: April 6, 2001

Time: 11:00 am

CBER Personnel: Victoria Tyson-Medlock
Louis Marzella
Jawahar Tiwari
Martin Green
Jooran Kim
Russell Fleischer

Company Personnel: Penelope Giles
Rachael Steiner
Jan Albrecht
Mark Laughlin
Mei-Hsiu Ling
Carol Morrow

INTRODUCTION

This call was scheduled to discuss the weight-based ribavirin dosing regimen that Schering would like approved with this supplement. This supplement was submitted to treat chronic hepatitis C (CHC) with a combination of ribavirin and PEG-Intron.

DISCUSSION

Dr. Jooran Kim asked the sponsor if they have any additional data in which patients were treated with — mg/day of ribavirin. The sponsor stated patients were treated with up to 1200 mg/day of ribavirin in study []. This study was submitted to the Rebetron NDA. The agency asked the sponsor to submit their additional PK/PD analysis of this study to this supplement because there are no pharmacokinetic data submitted for patients who received the — mg/day dose. The pharmacokinetic data submitted in this supplement is from a different study [] and involved a small number of patients. In addition there is no safety data at the — mg dose. Dr. Kim informed the sponsor that the relationship between weight and the level of absorption and clearance of ribavirin is unknown and how this may effect efficacy. The sponsor stated that they have done additional analyses of the data in patients weighing between

48 to 96 kgs. The agency asked the sponsor if there is a known relationship between weight and the clearance of ribavirin. The sponsor will submit information on this issue.

The agency informed the sponsor that the weight-based dosing claim will either be accepted or rejected after the data have been reviewed in more detail. As part of their post marketing commitments for the approval of PEG-Intron the sponsor submitted a protocol to evaluate treating African-American patients with the PEG-Intron and ribavirin combination using the weight-based dosage proposal for ribavirin.

Within this post-marketing study, the agency recommended that a subset pharmacokinetic study be considered with full pharmacokinetic profiles, in which patients receive the — mg dose of ribavirin in combination with 1.5µg PEG-Intron to support their weight-based dosing proposal. The sponsor does not have concrete plans at the moment to conduct a pharmacokinetic study but stated that they will consider the agency's recommendation.

To better assess the risk to benefit of different doses of ribavirin Dr. Louis Marzella asked the sponsor to conduct a re-analysis of the Phase 3 data for safety and efficacy with several cut off increments for the ribavirin dose. This analysis should include a global look at the safety and efficacy of the combination and include laboratory parameters, adverse events, and hemoglobin levels. The agency informed the sponsor that this analysis can include other amputations but must include the primary endpoint prospectively specified, last observation carried forward. The agency stressed the importance of submitting this information in timely manner because this supplement was granted a six month priority review.

The teleconference was concluded.

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Our STN: BL 103949/5002

Nicholas J. Pelliccione, Ph.D.
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

APR 05 2001

Dear Dr. Pelliccione:

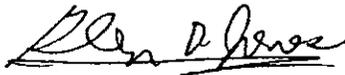
This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your supplement dated February 5, 2001, for Peginterferon alfa-2b to include its use in combination with ribavirin for the treatment of chronic hepatitis C, to determine its acceptability for filing. In accordance with 21 CFR 601.2(a) the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the supplement, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 827-5101.

Sincerely yours,



Glen D. Jones, Ph.D.
Director
Division of Application
Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

TysonMedlock, Victoria

From: Rosenberg, Amy
Sent: Wednesday, March 21, 2001 6:37 PM
To: TysonMedlock, Victoria; Cherney, Barry
Cc: Fleischer, Russell D
Subject: RE: PCR consult reviewer

Vicky,
Ralph Bernstein will take this on. Thanks.

-----Original Message-----

From: TysonMedlock, Victoria
Sent: Wednesday, March 21, 2001 1:27 PM
To: Rosenberg, Amy; Cherney, Barry
Cc: Fleischer, Russell D
Subject: PCR consult reviewer
Importance: High

Hello,

I am the regulatory coordinator assigned to Schering PEG-Intron and Ribavirin supplement, 103949/5002 for the treatment of HCV. We would like to have a product reviewer assigned to this supplement to determine the sensitivity of [] HCV-RNA PCR assay. I will get the number of the Master File from CBER and they will forward a copy of their review of [] assay. (I remember someone named Indira I think attending a meeting about [] PCR assay a while ago along with another reviewer) thanks a lot vicky

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

DATE: March 21, 2001
FROM: Victoria Tyson-Medlock
TO: Amy Rosenberg 
PEG-Intron and Ribavirin Supplement
103949/5002

Dr. Amy Rosenberg assigned Dr. Ralph Bernstein as a consult product reviewer to supplement 103949/5002, PEG-Intron and Ribavirin.

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Telecon Record

Date: March 20, 2001
Time: 4:00 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner and requested that they submit a CD with 2 PK/PD study for Dr. Jooran Kim.

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

DATE: March 19, 2001

FROM: Victoria Tyson-Medlock
Consumer Safety Officer
OTRR/DARP/AAB

SUBJECT: Filing Meeting Minutes
Schering Biologics License Supplement
PEG-Intron and Ribavirin 103949/5002
3:00-3:40
WOC I Room 236

TO: BLs 103949/5002

INTRODCUTION:

Schering Corporation submitted a supplement to their PEG-Intron Biologics License Application (BLA) to treat hepatitis C with a combination of PEG-Intron and Ribavirin. This meeting was held to decide if this supplement is acceptable for filing.

DISCUSSION:

Dr. Marzella stated that this supplement is acceptable for filing based on a review of the SAS data sets and the efficacy data. However, the review team will review the results of the serum HCV-RNA PCR results before making a final decision.

Drs. Louis Marzella, William Schwieterman, Mr. Michael Fauntleroy and Robert Yetter met to discuss the remote data entry system that was used to collect information on the case report forms in the study used to support this indication. On March 16, 2001, the sponsor submitted electronic and hard copies of the safety data and the HCV-RNA serum PCR results conducted by []

The review team was advised to review the safety and efficacy data very closely because the results may be marginal. []'s assay is not a validated assay. Schering has made the claim that []'s, HCV-RNA assay is sensitive to [] copies/mL however the agency does not agree. The Center for Drugs Evaluation and Research reviewed []'s PCR assay and stated that []'s assay is sensitive to [] copies/mL not

copies/ml. Mr. Russell Fleischer will send a copy of Dr. Battula's review of assay to Dr. Marzella. A product reviewer will be assigned to review assay and a consult may be requested by Dr. John Tyser's group. Schering is developing an internal PCR assay.

The agency asked the sponsor to submit Med Watch forms on the patients who experienced serious adverse events because the sponsor does not provide sufficient follow-up information on the patients

Dr. Schwieterman stated that there was a problem with Schering IL-10 trials in which they failed to report a serious adverse event. This event was a case of demyelinating disease that occurred in November, 1999 that was not reported to the agency until May, 2000. Dr. Marzella contacted the sponsor about this event and was informed that an internal committee decided that this event was not reportable.

Dr. Jooran Kim, the CDER consult clinical pharmacologist assigned to this supplement stated that the information submitted does not support weight-based dosing. The sponsor submitted a logistic regression model but no pharmacodynamic data. The sponsor submitted data from a pharmacokinetic study that enrolled 72 patients but different doses of PEG-Intron were administered and this is very different data. The agency questioned whether this model is validated and what the sponsor has done internally to support weight-based dosing of ribavirin. A teleconference will be scheduled to discuss this issue with Schering.

The issue was raised regarding the fact that PEG-Intron is licensed to treat HCV with a dose of 1.0 µg/kg and the sponsor proposes treating patients with a combination of 1.5 µg/kg of PEG-Intron and ribavirin. Dr. C J has a Schering sponsored study under IND to treat naïve, relapsers and non-responder HCV patients with PEG-Intron and ribavirin. During the Pre-BLA meeting held under IND on December 14, 2000, the sponsor was advised to revise this study to optimize peginterferon dosing. The agency has now asked the sponsor to submit a protocol to compare the 1.0 and 1.5 µg/kg doses of PEG-Intron in patients with HCV. This protocol was faxed to the agency and will reviewed and discussed with Schering.

Dr. Schwieterman raised the issue that this supplement may not be approved. Critical to the review of this supplement is the safety data, and the efficacy of the combination. This is an equivalence trial and an additional study may be required.



Telecon Record

Date: March 1, 2001
Time: 11:30 A.M.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner and requested one set of sections 2, 3, 6, and 8 of the PEG-Intron and ribavirin supplement for Dr. Jooran Kim the CDER clinical pharmacology consult. Ms. Steiner stated that the copies should arrive on Monday, March 5, 2001.

Appears This Way
On Original

TysonMedlock, Victoria

2-27-01-CDER consult

From: Kim, Jooran
Sent: Thursday, March 01, 2001 10:21 AM
To: TysonMedlock, Victoria
Subject: RE: PEG-Intron and Ribavirin Consult Request-103949/5002

Hi Victoria:

Could you please send me paper copies of those sections that were listed in the consult? I'd really appreciate it!

Thanks,
Jooran

-----Original Message-----

From: TysonMedlock, Victoria
Sent: Wednesday, February 28, 2001 8:46 AM
To: Kim, Jooran
Subject: RE: PEG-Intron and Ribavirin Consult Request-103949/5002

Hi Jooran,

I'll see if I have another site and send it to you. vicky

-----Original Message-----

From: Kim, Jooran
Sent: Tuesday, February 27, 2001 5:18 PM
To: TysonMedlock, Victoria
Subject: RE: PEG-Intron and Ribavirin Consult Request-103949/5002

Hi Vicki:

I'm the PK reviewer assigned to this consult. I can't seem to get into CBER's edr (when I doubleclick your webpage, I'm not getting through). Is there another way of getting there? Oddly, I can't seem to get there through the CDER edr. Thanks!

Jooran

-----Original Message-----

From: TysonMedlock, Victoria
Sent: Tuesday, February 27, 2001 4:45 PM
To: DeCicco, Anthony W
Cc: Kim, Jooran; Reynolds, Kellie S; Marzella, Libero
Subject: PEG-Intron and Ribavirin Consult Request-103949/5002
Importance: High

Good Afternoon,

here is the consult request for the PEG-Intron and Ribavirin supplement, as well as the location of the supplement in the electronic document room (EDR) and link for the supplement below. Thanks a lot for all of your help! vicky 7-5131

<< File: cderconsultrequest.doc >>

The electronic supplement from Schering has been successfully loaded in the EDR and is now available, located in the EDR_PROD\2001 BLA\ Folder as DCC# 42164. This is a supplement to the Original Submission STN# 103949 (99-1488).



Telecon Record

Date: February 28, 2001

Time: 11:00 a.m.

CBER Personnel: Victoria Tyson-Medlock
Patricia Hasemann
Louis Marzella
Jawahar Tiwari
Michael Fauntleroy

Company Personnel: Rachael Steiner
April Monge
Jean-Louis
Penny Giles
Joann W. Harvey
David Detoro
Peter Savino
Manuel Da Fonseca
Tracey Blazovic
Carolina Cubillos

Schering Corporation submitted a supplement to their PEG-Intron Biologics License Application (BLA) to treat chronic hepatitis C with a combination of PEG-Intron and ribavirin. The sponsor used a remote data entry system to collect the information in the case report forms (crf's) and therefore paper crf's do not exist. During the Pre-BLA meeting held on December 14, 2000, the sponsor acknowledged problems creating crf's in PDF format from the electronic data, but stated that they can submit the data in a summarized format.

The CRF do not capture the primary efficacy data. The primary efficacy outcome is loss of detection of HCV RNA; viral genotype (1 vs. non-1) is an important covariate in the primary efficacy analysis. Patient specimens were sent from the study center to a central laboratory [] for viral assays. The laboratory sent the results to the sponsor electronically for direct transfer to the study SAS data base. The central lab also sent the results of viral assays to the investigator who filed the results in

the patient's clinical record. The protocol did not require that the patients be informed of results of viral assays during the treatment period (except at baseline to confirm HCV viremia) and the CRF were not designed to capture the results of the assays either in treatment or post-treatment period.

The agency would like to see a validation of the process of data transfer from the central lab to the SAS database. The agency would also like to receive a copy of the HCV titers and genotype primary data from the central laboratory. This teleconference was held to discuss the appropriate format for the submission.

The sponsor agreed to submit the following:

- ◆ [] laboratory report which contains the study site number, patient number, initial visit data name, internal number, [] laboratory number, identifier sample data, HCV genotype at baseline and HCV titers at baseline, during treatment and in post-treatment period. If the PCR results are $< 10^3$ copies/mL, they are reported as negative and if positive the viral load is reported. The report will also states if there was insufficient sample to conduct PCR. A validation protocol will also be submitted that was used to validate data transfer from [] to Schering and a clear detailed explanation of all quality control steps. This information will be submitted within two weeks from March 2, 2001.
- ◆ SAS transport files of the raw data in tabular form with patient identification number and patient identifier number organized by study site.

Appears This Way
On Original

FEB 26 2001

Joseph F. Lamendola, Ph.D.
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

SUBMISSION TRACKING NUMBER (STN) BL 103949/5002 has been assigned to your recent supplement to your biologics license application for Peginterferon alfa-2b to include its use in combination with ribavirin for the treatment of chronic hepatitis C, received on February 5, 2001.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). Please refer to the FDA Draft Guidance for Industry: Recommendations for Complying With the Pediatric Rule (21 CFR 314.55(a) and 601.27(a)) (November 2000), available at <http://www.fda.gov/cber/gdlns/pedrule.pdf>. If you have not already fulfilled the requirements of 21 CFR 601.27, please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 601.27.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 601.27 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

All future correspondence or supportive data relating to this supplemental application should bear the above STN and be addressed to the Director, Division of Application Review and Policy, Office of Therapeutics Research and Review, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20852-1448.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need to discuss the technical aspects of this supplement, you may obtain the name of the chairperson of the review committee by contacting this division at 301-827-5101.

Any questions concerning administrative or procedural matters should also be directed to this division.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

bcc: STN File
Director, Product Release Staff, HFM-672
Red Folder
Victoria Tyson-Medlock, HFM-588
Louis Marzella, HFM-582

OTRR/DARP: A.Williams:2-8-01:Dixon:2-13-01:2.16.01:2.20.01
(S:\STN 2001\103949.5002.pas.doc)

COMMUNICATION TYPE:

LETTER: Acknowledgement Letter (ACK)

Summary Text: STN Assignment – Pre Approval (ZPAS)

**FILE
COPY**

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR	Williams	2-21-01	DARP	DIXON	2-26-01			
DARP	Amess	2-21-01						
DARP	Dix Dixon	2-26-01						

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

DATE: February 21, 2001

FROM: Victoria Tyson-Medlock
Consumer Safety Officer
OTRR/DARP/AAB

SUBJECT: First Committee Meeting
Schering-Biologics License Supplement
Peg-Intron and Ribavirin
STN 103949/5002
11:00-12:00
WOC I Room 350N

TO: Biologics License Supplement File

INTRODCUTION:

This first committee meeting was held to discuss Schering's Biologics License Supplement (BLs), submission tracking number 103949/5002, that was submitted to treat chronic hepatitis C with a combination of PEG-Intron and ribavirin. The sponsor plans to treat chronic hepatitis C with 1.5µg/kg of PEG-Intron and 800 — mgs of ribavirin. This supplement was received on February 5, 2001, and designated as a priority, six month review.

A copy of the roles and the responsibilities of the Chairman and regulatory coordinator was distributed. The review team was assigned and consist of:

Louis Marzella-Clinical Reviewer and Chairman
Anne Pilaro-Pharmacology/Toxicology Reviewer
Jawahar Tiwari-Statistical Reviewer
Patricia Hasemann-Bioresearch Monitoring Reviewer
Victoria Tyson-Medlock-Regulatory Coordinator

The milestones for this supplement were reviewed:

Committee Assignment	February 5, 2001-Assigned February 5, 2001
First Committee Meeting	February 26, 2001-Held February 21, 2001
Filing Meeting	March 22, 2001
Filing Action	April 6, 2001
First Action Due Date	August 7, 2001

This supplement was submitted in paper and electronically and can be assessed through the Electronic Document Room (EDR). Routing instructions were sent to the document control center but the paper copies of this submission have not been received by some of the review team. A call was placed to Schering and two sets of volumes 11-21 and one set of volume 22 were requested for Dr. Tiwari and Patricia Hasemann. Ms. Rachael Steiner stated that the additional copies should be received by Friday, February 23, 2001. Dates will be proposed for a training session for the review team to go over accessing the BLs through the EDR.

Pharmacology/Toxicology:

There are two pharmacology/toxicology studies in this supplement. CBER was notified by DAVDP/CDE/CDER earlier this week that eight monkey deaths were observed in one of the pharm/tox studies submitted to CDER's IND [] which uses [] Three of five monkeys treated with PEG-IFN (353 µg/kg) and the present version of ribavirin at a dose of 50 mg/kg died. Additional deaths were observed in 1/5, 1/5, and 3/5 monkeys treated with the new, alanine ester form of ribavirin at 15, 50, and 75 mg/kg/day, respectively. The deaths were due to bone marrow toxicities, i.e. suppression of neutrophil production, and to development of opportunistic infections (organism/s unknown). These findings were similar to those observed in two monkey toxicity studies which were submitted to the sBLA for PEG-IFN and ribavirin, in which deaths were observed in monkeys treated with PEG-IFN in combination with 50 mg/kg/day ribavirin. In studies conducted with ribavirin alone, rats also had severe toxicities in doses equal to or greater than 80 mg/kg of ribavirin. Animals developed thymic atrophy. Dr. Anne Pilaro stated that the doses of both the PEG-IFN and ribavirin used in the monkey pharm/tox studies were much higher than what would be administered clinically, and the affinity for PEG-Intron is lower in monkeys. The results of the pharm/tox studies in monkeys with the combination of PEG-IFN and ribavirin are included in the sBLA submission; the toxicity study using the alanine ester form is supportive of these findings, but is considered unrelated to the safety of the combination proposed currently. The lack of inclusion of these study data will not be considered a refusal-to-file issue.

Clinical:

The case report forms (crf's) were discussed. The sponsor used a remote data entry system to collect this information. There are no paper copies and the agency does not

have the case report forms to cross check and validate the data. Schering is willing to submit the data on the crf's from the contractor. The agency needs reassurance that the data in the BLs accurately reflects the information collected. A teleconference will be scheduled to request that the raw data be submitted within the next two weeks.

Drs. Louis Marzella and Jawahar Tiwari will contact Schering to get information on how the PCR samples are transferred from the clinical center to the central laboratory and to Schering, and how the data was collected at Schering.

Ms. Patricia Hasemann stated that an assignment has been issued to investigate a complaint by a patient with HCH who had a liver biopsy and then was excluded from participating in the study because of prior antidepressant use. Schering runs a screening protocol.

Schering will be asked to submit MedWatch reports to the BLs that have been submitted to IND — as there is limited information in this submission.

Dr. Schwieterman advised the review team to review the data very closely. The p value of this study was 0.04 and PEG-Intron and ribavirin was compared to Rebetron. The point estimates were 523 percent for the high dose versus 46 percent for Rebetron. The ALT data correlates very well but the ratio of risk to benefit may be narrow. The review team was asked to review the minutes from a teleconference that was held to discuss statistical analysis plan. This study was stratified and adjusted based on two covariates, liver fibrosis and genotype. The primary data is on the genotype.

The ribavirin dose was fixed in this trial but the sponsor would like to license weight based dosing. The review team along with a CDER consultant (clinical pharmacologist) will determine whether weight based dosing is justified. A study under IND, [redacted] is evaluating fixed versus weight based dosing of ribavirin. These results may be required prior to approval of this supplement for weight-based dosing. Dr. Marzella will provide language for the CDER consult.

The review team was advised to review the adverse events very carefully. The review team noted that there are toxicities associated with this product. suppression of erythropoiesis, (red cell lineage), neutropenia, lymphopenia and anemia. There is also evidence of increased toxicities, fever, chills and muscle aches. Patients treated with the monotherapy experienced thrombocytopenia and neutropenia consistently across the genotypes.

PEG-Intron is not approved in Europe.

This is a very high profile product and the label will go out to millions of patients once Rebetron once Rebetron is unbundled.

The midcycle meeting will be scheduled for early May.

A pediatric advisory meeting will be held on April 23, 2001.

The National Consensus Conference will be held in 2002. A session on the history, morbidity and mortality will be held.

The meeting was adjourned.

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On Original*



Telecon Record

Date: February 21, 2001
Time: 3:20 p.m.
CBER Personnel: Victoria Tyson-Medlock
Company Personnel: Rachael Steiner

I called Ms. Steiner at Schering and requested two sets of 11-21 and one set of volume 22. This information was requested in the initial request for volumes of the BLA but somehow was not submitted.

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TysonMedlock, Victoria

From: Weiss, Karen
ent: Friday, February 16, 2001 11:25 AM
ro: TysonMedlock, Victoria
Subject: PegIntron + Ribavirin

This application will be designated as a 6 month priority review application.

karen

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On Original*

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

DATE: February 16, 2001
FROM: Victoria Tyson-Medlock
TO: Karen Weiss *KW*
PEG-Intron and Ribavirin Supplement
103949/5002

Dr. Karen Weiss designated this supplement 103949/5002, PEG-Intron and Ribavirin for the treatment of chronic hepatitis C for a priority review.

*Appears This Way
On Original*

REVIEW COMMITTEE ASSIGNED MEMORANDUM

Date: 2/5/01

STN: 103949.5002

Regulatory coordinator: Vicky Tyson-Medlock

Job Type: administrative/regulatory

Applicant: Schering Corporation

Product: PEG-Intron and RebetoI

Type of submission: Prior Approval Supplement

Purpose of submission: To treat chronic hepatitis C with a combination of 1.5 mcg/kg PEG-Intron once a week subcutaneously and > 10.6 mg/kg/day orally of RebetoI

Review time frame: 6 months

The review committee for this BLA/Supplement is as follows:

Chairperson: Louis Marzella

Job Type: Clinical

Reviewers:

Name

Administrative/Reg. Vicky Tyson-Medlock

BIMO Patricia Hasemann

Biostatistics Jawahar Tiwari

Clinical Louis Marzella

CMC

Epidemiology

Facility

Inspector

Labeling

Other

Pharm/Tox Anne Pilaro

Product

SOP

Consultative reviewers:

Reviewer Name:

Job Type:

Communications Memo Entered AH Date 2/14/01 QC LB Date 2-15-01

Revised by: O'Leary:10/30/00