

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125196**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125196/0 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Division: DAVP Stamp Date: 7-3-06 PDUFA Goal Date: 6-22-08

Proprietary Name: PegIntron REDIPEN/REBETOL

Generic Name: Peginterferon alfa-2b and Ribavirin, USP

Dosage Form: subcutaneous injection and capsules

Applicant/Sponsor: Schering Corporation

Indication(s) previously approved (please complete this question for supplements only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

**Q1:** Is this application in response to a PREA PMC? Yes  No  Please proceed to question two.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC?

- Yes. **Skip to signature block.**
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

- (a) NEW  active ingredient(s);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*
- (b) No.  PREA does not apply. **Skip to signature block.**

\* **Note: SE5, SE6, and SE7 submissions may also trigger PREA.**

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

**Q3:** Is this an orphan indication?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for the remaining pediatric subpopulations (Complete Sections C and F)
  - Completed for some or all pediatric subpopulations (Complete Sections D and F)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E and F)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>A</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
X	Other	0 yr. __ mo.	3 yr. 0 mo.	X	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? X No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage? X No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**[#]** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - X Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**[\*]** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**[†]** Ineffective or unsafe:

- Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

**[Δ] Formulation failed:**

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †	
				Ready for Approval in Adults	Need additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
Population	minimum	maximum						
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
X Other	3 yr. __ mo.	17 yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	17 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): <u>June 30, 2008</u>								

Are the indicated age ranges (above) based on weight (kg)?  No; X Yes.

Are the indicated age ranges (above) based on Tanner Stage? X No;  Yes.

\* Other Reason: supplement to expand the indication to include pediatric patients 3-17 years of age will be submitted by June 30, 2008

PeRC Pediatric Plan Template completed and attached.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	17 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	17 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	17 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

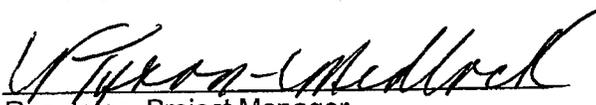
Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete another Pediatric Page for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.*

This page was completed by:

  
Regulatory Project Manager

(Revised: 3/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # 125196/0 NDA #	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: PegIntron and REBETOL Established Name: Peginterferon alfa-2b and Ribavirin, USP Dosage Form: parenteral, oral capsules		Applicant: Schering Corporation
RPM: Victoria Tyson-Medlock		Division: DAVP      Phone # 301-796-0827
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		June 22, 2008
❖ Action Goal Date (if different)		June 6, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None CR-4-7-07 and 4-1-08
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  NDAs and NDA Supplements: <input type="checkbox"/> OTC drug  Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                     <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> <li>NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> <li>NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>NDA: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>NDA: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>NDA: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>)</li> <li>[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified  <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p><b>Summary Reviews</b></p>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	April 30, 2008
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	June 6, 2008
<p><b>Labeling</b></p>	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	June 3, 2008
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	July 3, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	June 3, 2008
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	July 3, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	February 8, 2008
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (indicate date of each review)	August 9, 2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (Include certification.)	<input type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for post-marketing commitments (if located elsewhere in package, state where located)</li> <li>• Incoming submission documenting commitment</li> </ul>	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (indicate date; approvals only)</li> <li>• Pre-NDA/BLA meeting (indicate date)</li> <li>• EOP2 meeting (indicate date)</li> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	<input type="checkbox"/> No mtg <input type="checkbox"/> No mtg
❖ Advisory Committee Meeting <ul style="list-style-type: none"> <li>• Date of Meeting</li> <li>• 48-hour alert or minutes, if available</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (indicate date for each review)	March 26, 2008 and April 3, 2008
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li>• <input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</li> <li>• <input type="checkbox"/> Review &amp; FONSI (indicate date of review)</li> <li>• <input type="checkbox"/> Review &amp; Environmental Impact Statement (indicate date of each review)</li> </ul>	August 23, 2006
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review)	<input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include BER printout)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	March 22, 2007
<ul style="list-style-type: none"> <li>• Facility review (indicate date(s))</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (indicate date completed, must be within 60 days prior to AP)</li> </ul>	<input checked="" type="checkbox"/> Requested May 6, 2008 <input checked="" type="checkbox"/> Accepted May 27, 2008 <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	May 1, 2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (indicate location/date if incorporated into another review)	N/A
❖ Risk Management Plan review(s) (including those by OSE) (indicate location/date if incorporated into another review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>• Clinical Studies</li> <li>• Bioequivalence Studies</li> <li>• Clin Pharm Studies</li> </ul>	
❖ Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None

Comment [1]

### Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**TysonMedlock, Victoria**

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**From:** Kiel, Hea S  
Tuesday, May 27, 2008 2:42 PM  
TysonMedlock, Victoria  
**Cc:** CDER-TB-EER  
**Subject:** FW: STN 125196/0--PegIntron and REBETOL Co-packaged BLA-EER Request

Victoria,

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request below. There are no pending or ongoing compliance actions to prevent approval of STN 125196/0 at this time.

The status is as follows:

<u>FIRM Name</u>	<u>EI Number</u>	<u>Inspection Date</u>	<u>Classification</u>	<u>Profile</u>
(1) Schering Plough LTD :Final 4/29/05 Singapore	3004611169	8/16 ~ 8/26/04 60 Tuas West Drive	NAI	TRP:AC on 8/26/04
(2) Schering Corp. v, TCM on 7/27/07 2000 Galloping Hill Rd. Kenilworth, NJ 07033	2210048	7/5 ~ 27/07	NAI	BTP, TTR, LIQ, OIN,
(3) [REDACTED]		3/19 ~ 26/07	NAI	BTP:AC :initial on
(4) Schering Plough (Brinny) Co. 8/25/05 Inneshannon, County Cork Ireland	3002808087 (9616653)	8/15 ~ 25/05	VAI	BTP, TRP:AC on
(5) Schering Plough Products, LLC TTR:OT: Final AC Piedco Industrial Park, Carr # 183 Piedras, PR 00771	2650155	2/13 ~ 27/07	NAI	CHG, CTX, TCM,

\* Firm is operating under consent decree C02-02397 dated 5/20/02; product approved on a product by product basis;

Current Status is Acceptable

(6)

9/12 ~ 22/05

NAI SVS:AC on

HeaSuk Kiel  
Consumer Safety Officer  
FDA/CDER/OC/DMPQ/HFD-323  
Phone: 301-796-3246  
Fax: 301-847-8741

---

**From:** TysonMedlock, Victoria  
**Sent:** Tuesday, May 06, 2008 3:01 PM  
**To:** CDER-TB-EER  
**Cc:** Clark-Stuart, Michelle; Randazzo, Giuseppe  
**Subject:** STN 125196/0--PegIntron and REBETOL Co-packaged BLA-EER Request  
**Importance:** High

Hello,

Please provide compliance checks for the following firms that are manufacturing sites (steps performed at site are listed in the sites below) for this BLA: **NOTE:** there are two products co-packaged- peginterferon alfa-2b (redipen) & rebetol (capsules) for the treatment of chronic hepatitis C.

1) Schering-Plough LTD., Singapore Branch; storage & ID testing of DS; packaging component preparation & sterilization; QC testing & release of excipients & packaging components; DP mfr. (compounding, sterile filling, lyophilization, & inspection); in-process control testing; labeling & packaging of cartridges; storage of bulk packaged labeled cartridges; QC testing & release of bulk cartridges; strength confirmation testing of finished cartridges sampled after labeling; stability testing of finished cartridges; packaging of labeled cartridges for shipment to the pen assembly site; & back-up site for QC Bioassay release & stability testing of peginterferon alfa-2b vials mfr'd. at SP Brinny & [REDACTED] for peginterferon alfa-2b redipen.

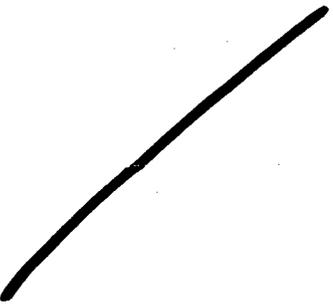
60 Tuas West Drive  
Singapore 638413  
FEI# 3004611169

2) Schering Corp. (secondary rebetol capsule packaging); final labeling &

packaging of finished product & diluent (sterile WFI); storage of bulk packaged labeled cartridges; identification testing of bulk cartridges; assembly of cartridge into pens including in-process testing; QC release of finished pens; final labeling & packaging of finished pens; final release of labeled & packaged pen; storage of final labeled & packaged pens; and distribution of final labeled & packaged pens in US for **peginterferon alfa-2b redipen and peginterferon alfa-2b powder for injection vials.**

2000 Galloping Hill Rd.  
Kenilworth, NJ 07033  
FEI# 2210048

3)



4) Schering Plough - Brinny; DS manufacture [mfr], (raw material testing, synthesis, &, purification); DP mfr. (excipient testing, compounding, sterile filling, &, lyophilization); in-process controls testing; DS & DP release and stability testing for **peginterferon alfa-2b powder for injection vials.**

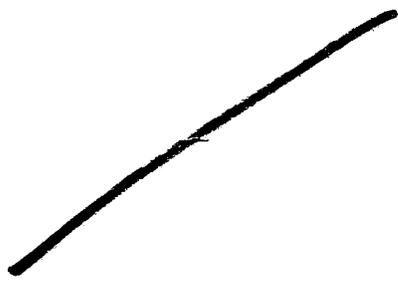


Brinny  
Innishannon Cork, Ireland  
FEI# 3002808087

5) Schering Plough (manufacturing, packaging, & control operations)

Pas Piedras Operations  
Pridco Industrial Park  
State Road # 183  
Las Piedras, PR 00771  
FEI# 2650155

6)



*We issued a Complete Response Letter on April 4, 2008, but are now ready to approve this BLA. Thanks Vicky 6-0827*



**COMPLETE RESPONSE**

Our STN: BL 125196/0

Schering Corporation  
Attention: Rachael Steiner  
Associate Director and Liaison  
Global Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

**April 4, 2008**

Dear Ms. Steiner:

This letter is in regard to the supplement to your biologics license application, dated June 28, 2006, received July 3, 2006, submitted under section 351 of the Public Health Service Act for PegIntron™ and REBETOL® to provide the products co-packaged, submitted under section 351 of the Public Health Service Act.

We acknowledge receipt of your amendments dated April 17, 2007, October 3, 2007, and March 31, 2008.

We have completed the review of your supplement. Our review finds that the information and data submitted are inadequate for final approval action at this time. The deficiencies are as follows:

We acknowledge receipt of the revised package insert and Medication Guide for the PegIntron™/REBETOL® Combo Pack. However, at this time we have not come to an agreement on labeling.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm> ).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; or (3) withdraw the supplement.

Our review clock has stopped with the issuance of this letter. Any amendment should respond to all deficiencies listed. We will not start the review clock until you have addressed all deficiencies.

If you have any questions, please contact the Regulatory Project Manager,  
Victoria Tyson-Medlock, at (301) 796-0827.

Sincerely,

A handwritten signature in black ink, appearing to read "Debra Birnkrant". The signature is fluid and cursive, with a large loop at the end.

Debra Birnkrant, M.D.

Director

Division of Antiviral Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** October 26, 2007  
**TIME:** 2:00 p.m.  
**LOCATION:** WO Conference Room 6378  
**APPLICATION:** STN 125196/0  
**DRUG NAME:** PEG-Intron and Ribavirin  
**TYPE OF MEETING:** Advice/Information Request

**FDA Participants:**

Victoria Tyson-Medlock, DAVP, Regulatory Project Manager

**Schering Participants:**

Rachael Steiner, Regulatory Affairs Associate

**DISCUSSION POINTS:**

Ms. Steiner called to discuss the October 3, 2007, response to our April 10, 2007, complete response letter, that was received on October 5, 2007. The Division issued an acknowledgment of the complete response letter to Schering based on the fact that the resubmission contained labeling only and was categorized as a Class 1 resubmission with a new PDUFA due date of December 5, 2007. However, the labeling that will be provided with the co-packaged products cross references the weight-based dosing of Ribavirin that is under review in STN 103949/5123. Therefore, the complete response will be classified as a Class 2 resubmission and a revised acknowledgment letter will be issued with a new PDUDA due date of April 5, 2008.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
5515 Security Lane  
Rockville MD 20852-1448

Date: ~~16~~ March 2007

To: Administrative File, STN 125196/0

From: Michelle Y. Clark-Stuart, MGA, MT (ASCP), Reviewer, CDER/OC/DMPQ/TRFB, HFD-328 *myl - 3/21/07*

Through: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328 *PH 3/21/07*

Subject: Review Memo: Biological License Application (BLA): BLA-Peginterferon alfa-2b and Ribavirin co-packaged (see STN 103949/0 and 103949/5002 for clinical data).

US License # 0994

Applicant Schering Corporation

Product peginterferon alfa-2b co-packaged with ribavirin

Indication Chronic hepatitis C

Due date: 3 May 2007

**Recommendation:** The information related to the co-packaging of these two approved Drug Products has been reviewed. There are no changes to equipment, facilities, or sterility assurance. The submission is recommended for approval.

### Review Summary

Schering has submitted this BLA to allow for revisions to the BLA-Peginterferon alfa-2b and Ribavirin co-packaged (see STN 103949/0 and 103949/5002 for clinical data).

The peginterferon alfa-2b co-packaged with ribavirin is supplied in the following dosage form: lyophilized Powder/Capsules for subcutaneous/oral administration. The strengths for this product is 50, 80, 120, 150 mcg/0.5/200mg.

Portions of the Rebetol<sup>®</sup> Capsule NDA 20-903 and the Peg-Intron<sup>®</sup> (Redipen) BLA 103949 are included in this submission 125196/0 for the co-packaging of these two drugs.

STN 125196/0, Schering Corporation

Schering submitted an electronic submission, only for information relevant to the CMC sections in support of this submission.

Products Affected

peginterferon alfa-2b co-packaged with ribavirin [REDACTED]

Review Narrative

The manufacture of Rebetol capsules and sites of manufacture, packaging, and control operations remain the same as provided in the approved NDA 20-903.

The manufacturing process for the PEG-Intron<sup>®</sup> Redipen product including sites of manufacture, packaging, and control operations remain the same as provided in the approved BLA 103949.

Co-packaging of these two approved products is the subject of this BLA. The co-packing allows for a patient convenience package for the treatment of chronic hepatitis C under the proprietary name of [REDACTED]. This patient convenience package requires revised product labeling including a Product Information Sheet, Medication Guide, PEG-Intron<sup>®</sup> labels, Rebetol bottle labels, and [REDACTED] carton labels.

Review Comment

The reason for this submission does not require a TFRB review of attributes of sterility assurance since the approved manufacturing processes have not changed.

Satisfactory

Summary packaging and container/closure descriptions for ribavirin capsule blister packs are adequate. A process flow chart is submitted. There are no changes to the components from what was previously approved.

Satisfactory

The manufacturing Process for PEG-Intron<sup>®</sup> Redipen (flow chart) is provided in the submission. Summary container/closure information is adequately described in this submission and figures of this approved system are also provided. There are no changes to the process from what was previously approved.

Satisfactory

The remainder of this submission relates to labeling issues (revised product labeling including a Product Information Sheet, Medication Guide, PEG-Intron<sup>®</sup> labels, Rebetol bottle labels, and [REDACTED] carton labels) and is deferred to other members of the review team for assessment.

**Environmental Assessment**

In accordance with 21 CFR 25.31(c), an Environmental Assessment is not required for this submission. Action on this submission will not alter significantly the concentration or distribution of the substance, its metabolites, or its degradation products in the environment.

is in compliance with the categorical exclusion criteria listed in 21 CFR 25.31(c), and no extraordinary circumstances exist.

**cGMP Status**

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the Therapeutic Biologic-EER request below. There are no pending or ongoing compliance actions to prevent approval of STN 125196/0 at this time.

The following are the current status for the submitted sites:

	<b>Manufacturer</b>	<b>FEI No.</b>	<b>Last EI DATE</b>	<b>EIR Classification</b>
1	Schering Plough LTD, Singapore	3004611169	8/16 - 8/26/04	NAI
2	Schering Corp. Kinilworth, NJ	2210048	5/3 - 25/2006	NAI
3			9/12 - 22/2005	VAI
4	Schering Plough - ( Brinny) Co. Inneshannon Cork, Ireland	3002808087	8/15 - 8/25/2005	VAI
5	Schering Plough Products, LLC	2650155	3/6 - 5/5/2006	VAI
6			9/12/ - 9/22/2005	NAI

**Conclusion**

- I. The submission was reviewed against existing regulations and guidelines for conformance and was found acceptable. The submission is recommended for approval.

STN 125196/0, Schering Corporation

- II. The summary portions of this BLA were the only sections requiring TFRB review as the manufacturing processes for both components of the co-packaged products remain the same as approved.
- III. No inspectional items were identified from this review.

Appears This Way  
On Original

cc: HFD-328, Hughes  
HFD-328, Clark-Stuart  
HFD-328, TFRB Blue Files (STN 125196)

Archived File: S:\archive\BLA\125196\125196.0.rev.mem.BLA.03-20-07.doc



**Date:** January 17, 2007

**BLA:** 125196/0

**Drug:** PEG-Intron and Ribavirin

**To:** Rachael Steiner

**Sponsor:** Schering Corporation

**From:** Victoria Tyson-Medlock, Regulatory Project Manager

**Through:** Jin hai Wang, Ph.D., Quality Reviewer, DTP  
Ko-yu Lo, Ph.D., Quality Reviewer, ONDQA  
Scott Proestel, M.D., Medical Officer, DAVP  
Laura Pincock, Pharm D., Safety Evaluator, DMETS

**Concurrence:** Elizabeth Shores, Ph.D., Quality Team Leader, DTP  
Norman Schmuft, Ph.D., Quality Team Leader, ONDQA  
Nora Roselle, Pharm D., Safety Evaluator Team Leader, DMETS  
Katherine Laessig, M.D., Medical Team Leader, DAVP

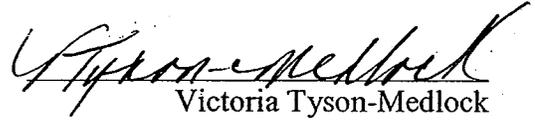
**Subject:** BLA 125196/0- Trade name for co-packaged PegIntron™ and Rebetol®

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The following comments are being conveyed to you on behalf of the review team. Please refer to your BLA 125196/0 submitted to co-package PegIntron™ (Peginterferon alfa-2b) and Rebetol® (Ribavirin, USP). Specifically, the trade name proposed for the co-packaged products, PegIntron/Rebetol Combo Pack. We have reviewed the proposed trade name and have the following comments:

The Division of Antiviral Products (DAVP) in conjunction with the Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing Advertising and Communications (DDMAC) reviewed the proprietary name PegIntron/Rebetol Combo Pack. DAVP, DDMAC, and DMETS have determined that the proposed proprietary name is acceptable. However, there is concern that the proposed name, PegIntron/Rebetol Combo Pack, is very long and some prescribers and/or computer systems and printers may find it difficult to fit the name on a prescription, in the existing data fields or on a prescription label. The name may be abbreviated to make it fit in these systems. We are concerned that such abbreviations may pose a problem; however, we are unable to ascertain what abbreviations may be used. Thus we are unable to evaluate the potential problems that abbreviations of this name might pose. Please be aware of the likelihood that abbreviations will be used, and take steps to reduce the potential for the name to be abbreviated.

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me at 301-796-0827 if you have any questions regarding the contents of this transmission.



Victoria Tyson-Medlock  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

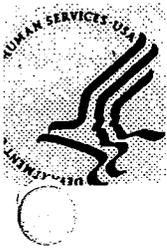
Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, we may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 796-0827.

Sincerely,

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products  
Food and Drug Administration  
Silver Spring, MD 20903

**Date:** January 12, 2007  
**BLA:** 125196/0  
**Drug:** PEG-Intron and Ribavirin  
**To:** Rachael Steiner  
**Sponsor:** Schering Corporation  
**Through:** Scott Proestel, M.D., Acting Team Leader, DAVP  
Jin hai Wang, Ph.D., Quality Reviewer, DTP  
**Concurrence:** Elizabeth Shores, Ph.D., Quality Team Leader, DTP  
**Subject:** BLA 125196/0- labeling review

Please refer to your BLA 125196/0 submitted to co-package PEG-Intron and Ribavirin. The Division of Antiviral Products in conjunction with The Division of Medication Errors and Technical Support (DMETS) has reviewed the container and carton labels and the package insert and Medication Guide with a focus on safety issues relating to medication errors. DMETS has identified the following areas of improvement which may minimize potential error:

Labeling Review

- A. CONTAINER LABEL (REBETOL; 56 count, 70 count, 84 count, and 98 count)**
1. Increase the prominence of the REBETOL product strength, 200 mg, and relocate the product strength to immediately follow the established name. The product strength and net quantity of the bottle should be located away from each other to decrease the potential for confusion. Additionally, on the principal display panel, the product strength should have more prominence than the net quantity.
  2. Decrease the prominence of the "Rx Only" statement. As currently presented, it appears larger and distracts from the most important information on the principal display panel such as the proprietary name, established name, and product strength.
- B. CARTON LABELING (Trade name; each package contains 4 Redipens of the same strength with a corresponding quantity of REBETOL capsules)**
1. Include the statements "DISCARD THE UNUSED PORTIONS" (in reference to PegIntron) on all carton labeling for Trade name.

2. The current presentation of the proprietary name, Trade name, in conjunction with the two drug component names, PegIntron and REBETOL, and each stylistic logo is difficult to follow as currently displayed. DMETS recommends the following presentation, with all three of the proprietary names in the same font and style to increase readability:

Trade name containing:

4 X PegIntron REDIPEN units (Peginterferon alfa-2b) 150 mcg/0.5 mL

1 bottle of 84 capsules containing REBETOL (Ribavirin, USP) Capsules 200 mg

Additionally, DMETS notes that the current cartons look very similar with the exception of the thin color stripe highlighting the strength and quantities of the drug components. DMETS recommends that you increase the prominence of the strengths and quantities and continue to feature them in color blocking to more clearly differentiate between the available packages.

3. DMETS notes that the black font on the green background of the 80 mg strength is very difficult to read, particularly on the back panel featuring the UPC code. We recommend that you consider use of an alternate colored background or consider increasing the size of the font to increase readability of this important information.

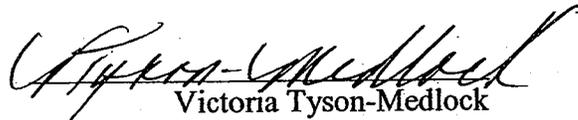
#### C. PACKAGE INSERT LABELING

1. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. We note that you use some of these error-prone abbreviations in your proposed labeling (e.g., trailing zeros or the mu symbol " $\mu$ "). The mu symbol should be revised to "mcg" because post-marketing experience has demonstrated that " $\mu$ g" is often misinterpreted as "mg". Additionally, the use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeroes and the mu symbol is specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list the mu symbol on their "Do Not Use" list. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. Thus, DMETS recommends that trailing zeroes and the mu symbol be removed from all labels and labeling (e.g., mcg rather than  $\mu$  and 1 mcg/kg rather than 1.0 mcg/kg).
2. Increase the prominence of the text, "once a week" in the package insert.

#### D. MEDICATION GUIDE

1. Increase the prominence of the text, "once a week" in the Medication Guide.

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me at 301-796-0827 if you have any questions regarding the contents of this transmission.



Victoria Tyson-Medlock  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Products  
Food and Drug Administration  
Silver Spring, MD 20903

**Date:** September 5, 2006  
**BLA:** 125196/0  
**Drug:** PEG-Intron and Ribavirin  
**To:** Rachael Steiner  
**Sponsor:** Schering Corporation  
**From:** Victoria Tyson-Medlock, Regulatory Project Manager  
**Through:** Jin hai Wang, Ph.D., Quality Reviewer, DTP  
**Concurrence:** Elizabeth Shores, Ph.D., Quality Team Leader, DTP  
Russell Fleischer, M.P.H., PA-C, Medical Team Leader, DAVP  
**Subject:** BLA 125196/0-Labeling-expiration dating

The following comments are being conveyed to you on behalf of the review team. Please refer to your BLA 125196/0 submitted to co-package PEG-Intron and Ribavirin.

**CMC Comments:**

Please add the expiration date for PEG-Intron and Rebetol on all labeling for the combination packaging. The expiration date should be placed under the trade names for each product and clearly visible so that the patient and pharmacist would be able to see the expiration date before opening the combination packs.

We are providing this above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me at 301-796-0827 if you have any questions regarding the contents of this transmission.

Victoria Tyson-Medlock  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

## TysonMedlock, Victoria

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**From:** Wang, Jin Hai  
**nt:** Wednesday, August 30, 2006 3:53 PM  
**:** TysonMedlock, Victoria  
**Cc:** Shores, Elizabeth  
**Subject:** RE: STN 125196/0-filing letter

Vicky,

No issues for filing. One comment for 74 day letter is to add Exp. date for Pegintron and Exp. date for Rebetol on the labeling of the Combo Packs under the name "Pegintron" or "Rebetol". Patients and Pharm should be able to know the Exp. dates before they open the Combo Packs.

Jinhai

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**From:** TysonMedlock, Victoria  
**Sent:** Tuesday, August 29, 2006 11:02 AM  
**To:** Proestel, Scott; Laessig, Katherine A; Clark-Stuart, Michelle; Uratani, Brenda W; Lo, Ko-yu; Schmuff, Norman R; Wang, Jin Hai; Shores, Elizabeth  
**Cc:** Behr, Virginia L  
**Subject:** STN 125196/0-filing letter  
**Importance:** High

Good morning,

please provide ESO or comments on the filing letter for the PEG-Intron and Ribavirin co-packaging BLA. The letter has to issue by this Friday the 1st. Thanks Vicky

<< File: 082506.filing letter with no deficiencies.doc >>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125196/0

Schering Corporation  
Attention: Rachael Steiner  
Associate Director and Liaison,  
Global Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

**August 30, 2006**

Dear Steiner:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated June 28, 2006, for PEG-Intron and RebetoI to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The user fee goal date is May 3, 2007. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

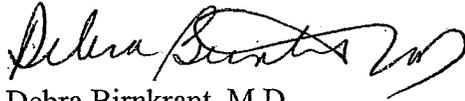
At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 796-0827.

Sincerely,

A handwritten signature in black ink, appearing to read "Debra Birnkrant" with a stylized flourish at the end.

Debra Birnkrant, M.D.

Director

Division of Antiviral Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

he package labeling will be reviewed by the quality reviewers from ONDQA (Ribavirin) and DTP (PEG-

tr  
he expiry of the co-packaged products will be based on the product with the shelf-life of the product with  
e shortest expiry.

**Appears This Way  
On Original**



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** August 9, 2006  
**TIME:** 9:45 a.m.  
**LOCATION:** WO Conference Room 6378  
**APPLICATION:** STN 125196/0  
**DRUG NAME:** PEG-Intron and Ribavirin  
**TYPE OF MEETING:** Information Request Telecon

**FDA Participants:**

Victoria Tyson-Medlock, DAVP, Regulatory Project Manager

**Schering Participants:**

Rachael Steiner, Regulatory Affairs Associate  
Margaret Casais, Regulatory Affairs, CMC

**DISCUSSION POINTS:**

I called Ms. Steiner and Casais and asked that they submit the following information to the BLA 125196/0 as soon as possible:

- A summary of the manufacturing process for PEG-Intron and Ribavirin, the facilities that will be responsible for co-packaging the products and the facilities for manufacture of the individual products with a list of the activities at the facilities.
- Debarment certification
- A request for categorical exclusion or environmental assessment



**MEMORANDUM: First Committee Meeting**

**DATE:** July 24, 2006

**BLS:** 125196/0

**BACKGROUND INFORMATION:**

In lieu of a face-to-face first committee meeting for this Biologics License Application submitted to provide PEG-Intron co-packaged with Rebetol (Pegylated Interferon alfa-2b and Ribavirin) Supplement, assigned STN 125196, the following information was sent to the review team:

This supplement was submitted on June 28, 2006, and received on July 3, 2006, to provide PEG-Intron co-packaged with Ribavirin. This is a Biologics License Application (BLA) with a 10-month review clock in the Division of Antiviral Products. Dr. Scott Proestel is the clinical reviewer and chairman, Jin hai Wang and Ko-yu Lo are the quality reviewers and Michelle Clark-Stuart is the quality and facility reviewer. The milestones are as follows:

- Committee assignment-July 17, 2006
- First committee meeting-July 24, 2006
- Filing meeting-August 17, 2006
- Filing action-September 1, 2006
- Deficiencies Identified-September 15, 2006
- First action due date-May 3, 2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125196/0

Schering Corporation  
Attention: Rachael Steiner  
Associate Director and Liaison,  
Global Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, NJ 07033

Dear Ms. Steiner:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

<b>Our Submission Tracking Number (STN):</b>	BL 125196/0
<b>Name of Biological Product:</b>	PEG-Intron AND REBETOL/ Peginterferon alfa-2b and Ribavirin:
<b>Indication:</b>	Treatment of chronic hepatitis C; to provide Peginterferon alfa-2b co-packaged Ribavirin
<b>Date of Application:</b>	June 28, 2006
<b>Date of Receipt:</b>	July 3, 2006
<b>User Fee Goal Date:</b>	May 3, 2007

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. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:  
<http://www.fda.gov/oc/datacouncil/spl.html>.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

Please cite the BLA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

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.

If you have any questions, please contact the Regulatory Project Manager, Victoria Tyson-Medlock, at (301) 796-0827.

Sincerely,



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