

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 22-206**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-206 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 12/13/07 PDUFA Goal Date: 10/13/08

HFD 580 Trade and generic names/dosage form: Rapaflo (silodisin)

Applicant: Watson Therapeutic Class: \_\_\_\_\_

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

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

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: \_\_\_\_\_ BPH

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA 22-206

Page 3

**This page was completed by:**

*[See appended electronic signature page]*

**Olga Salis**

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**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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

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Olga Salis  
2/5/2008 09:25:43 AM

### 1.3.3 DEBARMENT CERTIFICATION

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

*Susan Skara* Date 2-6-08

Susan Skara  
Senior Vice President  
Human Resources

*Paul Lang for* Date 02-06-2008

Kevin Barber, Ph.D., RAC, P.M.P.  
Executive Director  
Proprietary Regulatory Affairs

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-206 BLA #	NDA Supplement # 0 BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Rapaflo Established/Proper Name: silodosin Dosage Form: Capsules		Applicant: Watson Agent for Applicant (if applicable):
RPM: Olga Salis		Division: HD-580
<p><b>NDA:</b>                      NDA Application Type: <input checked="" 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)</p> <p>(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.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated                      Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		10/08/08
❖ 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 ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  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  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain:	2/3/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: 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> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: 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> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: 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> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: 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 type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, 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 If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs 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 checked="" 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> </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)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(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 the rest of the patent questions.*

*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).*

<p>(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?</p> <p>(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 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 OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>10/8/08</p>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) 10/08/08</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	<p>9/29/08</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>12/12/07</p>
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>Flomax, Uroxatral, Cardura</p>
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input type="checkbox"/> Medication Guide  <input type="checkbox"/> Patient Package Insert  <input type="checkbox"/> Instructions for Use  <input checked="" type="checkbox"/> None</p>

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
 Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	12/12/07
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 6/3/08 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 4/1/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 9/11/08 Maternal Health 9/11/08
<ul style="list-style-type: none"> <li>❖ Proprietary Name                     <ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	6/3/08 7/8/08
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM 2/7/08
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant in 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>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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 (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Postmarketing Requirement (PMR) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Postmarketing Commitment (PMC) Studies</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• PeRC ( <i>indicate date; approvals only</i> )	<input type="checkbox"/> Not applicable 2/13/08
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	<input type="checkbox"/> Not applicable 8/4/08
• Regulatory Briefing ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 7/23/06
• EOP2 meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 2/10/05
• Other (e.g., EOP2a, CMC pilot programs)	Advice Meeting 4/10/08
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/08/08
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/08/08
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	10/08/08
• Clinical review(s) ( <i>indicate date for each review</i> )	9/25/08 Filing review 2/8/08
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	Page 67 of MO review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Page 25 of MO review
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None OSE 8/11/08 QT-IRT 4/16/08
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> ) • REMS Memo ( <i>indicate date</i> ) • REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 8/04/08

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/3/08
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 8/7/08 Filing review 1/30/07
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	9/11/08
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 9/11/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ 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	<input type="checkbox"/> None 11/24/08
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/17/08
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 9/16/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input type="checkbox"/> Not needed 8/21/08
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None filing review ONDQA 1/29/08
❖ Environmental Assessment (check one) (original and supplemental applications)	Original
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	9/16/08 page 96 CMC review

<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)</li> </ul>	Date completed: 10/17/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:           <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

### 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 ADRA.

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/s/

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Margaret Kober  
10/14/2008 12:45:52 PM

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** August 1, 2008

**TO:** Olga Salis, Regulatory Project Manager  
Olivia Easley, M.D., Medical Officer  
Division of Reproductive and Urologic Products (DRUP)

**FROM:** Jose Javier Tavarez, M.S.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-206

**APPLICANT:** Watson Laboratories, Inc.

**DRUG:** Silodosin (Rapaflo™)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia (BPH)

**CONSULTATION REQUEST DATE:** February 8, 2008

**DIVISION ACTION GOAL DATE:** September 30, 2008

**PDUFA DATE:** October 13, 2008

## I. BACKGROUND

Clinical investigator inspections were requested at four clinical sites that performed studies for which the sponsor submitted data in NDA 22-206. In addition, a sponsor inspection was requested because Rapaflo is a new molecular entity product. The clinical investigator and sponsor inspections were conducted according to the Compliance Programs 7348.811 (Inspection Program for Clinical Investigators) and 7348.810 (Inspection Program for Sponsors, Contract Research Organizations and Monitors), respectively. The inspections covered work performed under protocols SI04009 and SI04010 entitled "A Multi-Center, Randomized, Double-Blind, Placebo Controlled, Parallel Evaluation of the Efficacy and Safety of Silodosin in the Treatment of the Signs and Symptoms of Benign Prostatic Hyperplasia."

Studies SI04009 and SI04010 were a multi-center, double-blind, placebo-controlled, parallel, 12-week treatment trials in male patients with signs and symptoms of BPH. Patients were randomized to receive either 2 placebo capsules or 2 silodosin 4 mg capsules (8 mg total), once daily, for 12 weeks. The primary efficacy endpoint of the studies was the baseline-to-endpoint change in the total score of the International Prostate Symptom Score (IPSS). The safety of Rapaflo was evaluated by routine monitoring of adverse events, clinical laboratory parameters, ECGs, and physical examinations.

**Basis for Site Selection:** Four clinical sites (Drs. Auerbach, Roper, Young and Meissner) were inspected. These four clinical sites were recommended for inspection because they enrolled the largest numbers of subjects in the two pivotal studies for this NDA. The goals of the inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

The sponsor site was inspected because Rapaflo is a new molecular entity product. The goals of the inspection included validation of submitted data and compliance of specific responsibilities of the sponsor of clinical studies with FDA regulations. Among the elements reviewed for compliance were data collection and handling, study monitoring procedures, and subject records and reports.

## II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)/# of subjects	Inspection Date	Final Classification
Stephen Auerbach, MD 400 Newport Center Drive Suite 501 Newport Beach, CA 92660	SI04009 28 subjects	3/5-6/2008	NAI
Ronald P. Roper, MD 55 Whitcher Street, Suite 250 Marietta, GA 30060	SI04009 32 subjects	3/3-10/2008	VAI
Douglas Young, MD 3720 Mission Avenue, Suite 18, Carmichael, CA 95608	SI04010 30 subjects	4/7-16/2008	VAI

Page 3 of 7 – NDA 22-206 Rapaflo  
 Summary Report of U.S. Inspections

Kurt G. Meissner, MD 8038 Wurzbach Road Suite 430 San Antonio, TX 78229	SI04010 26 subjects	4/29 – 5/1/2008	NAI
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Sponsor/Site	Protocol(s)	Inspection Date	Final Classification
Watson Laboratories, Inc. 577 Chipeta way Salt Lake City, Utah 84108	SI04009 SI04010	3/17-25/2008	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

**1. Dr. Stephen Auerbach  
 Newport Beach, CA**

a. What was inspected?

There were 28 subjects who participated in the study. The FDA investigator performed a complete review of study records for all 28 subjects enrolled in the study. Complete files were reviewed for all subjects including study regulatory records, case report forms (CRFs), and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the NDA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Auerbach complied with protocol-specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Data generated for protocol SI04009 at this clinical site appear acceptable for use in support of NDA 22-206.

**2. Dr. Ronald Roper**  
**Marietta, GA**

a. What was inspected?

A total of 64 subjects were screened, 32 subjects were randomized into the study and 31 subjects completed the study. The FDA investigator performed a complete review of study records for 16 subjects enrolled in the study. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. The FDA investigator reviewed the source documents and case report forms, and compared these with data listings provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

There were no significant inspectional findings that would adversely impact data acceptability. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. No underreporting of adverse events was noted. Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms.

In general, Dr. Roper complied with protocol specified requirements. However, there were several instances where the inspection documented that Dr. Roper was in noncompliance with regulations pertaining to protocol compliance, specifically:

Dr. Roper did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

- i. The protocol required that potential subjects be excluded from the study if they had a prostate-specific antigen (PSA) screening test greater than 10.0 ng/ml. In addition, subjects with a PSA between 4.0 and 10.0 should have had prostate cancer ruled out to the satisfaction of the clinical investigator. The inspection revealed that a PSA test was not performed for subjects 133011 and 133032 to determine whether these subjects were, in fact, eligible to participate in the study.
- ii. The protocol excluded potential subjects if they had an intravesical obstruction from any cause other than benign prostatic hyperplasia (BPH) including urethral stricture. Upon review of the subject 133034's medical records, Dr. Roper indicated to the FDA investigator that he could not determine whether the subject had an active intravesical obstruction prior to randomization. However, the subject was enrolled in the study.

c. Assessment of data integrity:

No underreporting of adverse events was noted. The review division may wish to exclude from efficacy analyses the subjects who failed the study eligibility criterion as stated above. Overall, data generated for protocol SI04009 at this clinical site appear acceptable for use in support of NDA 22-206.

**3. Dr. Douglas Young  
Carmichael, CA**

a. What was inspected?

A total of 75 subjects were screened, 30 subjects were randomized into the study and 24 subjects completed the study. The FDA investigator performed a complete review of study records for 15 subjects enrolled in the study. Complete files were reviewed including study regulatory records, CRFs, and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the NDA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Young complied with protocol specified requirements. However, there were several instances where the inspection documented that Dr. Young was in noncompliance with regulations pertaining to protocol compliance, specifically:

Dr. Young did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

- i. The Cumulative Adverse Events Log for subject 272065 documents an adverse event (orgasm, no semen) on 1/31/06; however, this adverse event was not recorded on the Adverse Event page of the case report form as required by the protocol.
- ii. The Cumulative Adverse Events Log for subject 272065 documents an adverse event (orgasm, no semen) on 1/31/06; however, Dr. Young did not initial this log to acknowledge this adverse event (specifically confirm intensity, study drug relationship, and seriousness) as required by the protocol.
- iii. Investigational product compliance was to be assessed for each study visit as required by the protocol. Investigational product compliance at Visit 7 and Visit 8 was not assessed for subject 272065.
- iv. The protocol required recording on the case report form, study drug dispensing for each visit. Study drug dispensing was not recorded on the case report form for subject 272065's Visit #7.

c. Assessment of data integrity:

No underreporting of adverse events was noted. Data generated for protocol SI04010 at this clinical site appear acceptable for use in support of NDA 22-206.

4. **Dr. Kurt Meissner**  
**Newport Beach, CA**

a. What was inspected?

A total of 38 subjects were screened, 26 subjects were randomized into the study and 25 subjects completed the study. The FDA investigator performed a complete review of study records for all 26 subjects enrolled in the study. Complete files were reviewed for all subjects including study regulatory records, CRFs, and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the NDA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Meissner complied with protocol specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

No underreporting of adverse events was noted. Data generated for protocol SI04010 at this clinical site appear acceptable for use in support of NDA 22-206.

5. **Watson Laboratories, Inc.**  
**Salt Lake City, Utah**

a. What was inspected?

The inspection covered work performed under protocols SI04009 and SI04010. The inspection reviewed the following: quality assurance and clinical operations, study monitoring procedures, data collection and handling, subject records and reports, participating clinical investigators, monitoring reports, CRFs, data collection, and study drug accountability. Drs. Auerbach, Roper, Young, and Meissner were among the clinical investigators for whom sponsor responsibilities were evaluated.

b. General observations/commentary:

In general, the sponsor adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. There were no significant inspectional findings that would adversely impact data acceptability.

c. Assessment of data integrity:

No underreporting of adverse events was noted. The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

As stated above, there were several instances where the inspection documented that Drs. Roper and Young were in noncompliance with regulations pertaining to protocol compliance. In general, for the four clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol.

No underreporting of adverse events was noted. Overall, data generated for protocols SI04009 and SI04010 at these clinical sites appear acceptable for use in support of NDA 22-206.

*{See appended electronic signature page}*

Jose Javier Tavarez, M.S.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Jose Tavarezpagan  
8/4/2008 09:51:00 AM  
CSO

Constance Lewin  
8/4/2008 12:32:14 PM  
MEDICAL OFFICER



**INFORMATION REQUEST LETTER**

IND 22-206

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RAPAFLOR<sup>TM</sup> (silodosin) Capsules, 4 mg and 8 mg.

The Division of Medication Error Prevention has reviewed your submission and has the following comments and recommendations:

**PROPRIETARY NAME**

1. The Division of Medication Error Prevention has no objections to the use of the proprietary name Rapaflo for this product.
2. If any of the proposed product characteristics are altered prior to approval of the product, the Division of Medication Error Prevention rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.
3. If the product approval is delayed beyond 90 days, the proposed name must be resubmitted for evaluation.

**CONTAINER LABELS**

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**b(4)**



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George Benson  
7/8/2008 03:10:23 PM



NDA 22-206

INFORMATION REQUEST LETTER

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for silodosin capsules, 4mg and 8mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1. The acceptance criterion for the unidentified impurities in the drug product specification is higher than the identification and qualification limits recommended in ICH Q3B(R2). The acceptance criteria for the unidentified impurities will either need to conform to the identification and qualification thresholds recommended in ICH Q3A or you will need to justify higher limits with qualification data.
2. Add \_\_\_\_\_ test to the release specification for the drug product. \_\_\_\_\_  
\_\_\_\_\_
3. Provide clarification for the equation used to determine the residual solvents present in the drug substance.
4. Provide information on the method used to determine \_\_\_\_\_ of the drug product. The method used for \_\_\_\_\_ was not provided in the NDA submission.

b(4)

b(4)

If you have any questions regarding the contents of this letter, call Scott N. Goldie, Ph.D.,  
Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Moo-Jhong Rhee  
6/3/2008 02:55:55 PM  
Chief, Branch III



INFORMATION REQUEST LETTER

NDA 22-206

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for silodosin capsules, 4mg and 8mg.

We also refer to your submission dated December 13, 2007.

We are reviewing the Clinical Pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The effects of severe hepatic insufficiency were not evaluated. \_\_\_\_\_
2. The renal insufficiency study (KMD-309) enrolled patients with estimated creatinine clearance (mean  $\pm$  SD) of  $39.2 \pm 9.6$  mL/min (range: 27 – 49 mL/min). This is consistent with moderate renal impairment instead of severe renal impairment (See Guidance For Industry, Pharmacokinetics in Patients With Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling (May 1998)). Therefore, there was about a 3-fold increase in the exposure of silodosin in patients with moderate renal insufficiency. Dosing recommendation for renal insufficiency (mild, moderate, and severe) will need to be addressed in the labeling following a thorough review.

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

b(4)

**APPEARS THIS WAY  
ON ORIGINAL**

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Margaret Kober  
4/23/2008 02:41:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-206

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your new drug application (NDA) dated Decemeber 12, 2007, received Decemeber 13, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for silodosin capsules, 4mg and 8mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 13, 2008.

We are providing the following comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Clinical Pharmacology

1. Co-administration of a strong CYP3A4 inhibitor, ketoconazole, with silodosin increased the exposure to silodosin by about 3- to 4-fold. b(4)
2. The effects of weak and moderate CYP3A4 inhibitors on silodosin exposure were not evaluated. Dosing recommendation in this setting will be a review issue.

Pharmacology/toxicology

1. A "probable" level of phototoxicity (2- to 4-fold) was observed in an *in vitro* study. An *in vivo* phototoxicity study and *in vitro* photo-genotoxicity studies should be performed and submitted during this review cycle. b(4)



NDA 22-206  
Page 3

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Acting Deputy Director  
Division of Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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George Benson  
2/25/2008 01:24:05 PM

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 22-206 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: Rapaflo  
Established Name: silodosin  
Strengths: Capsules, 4mg and 8mg

Applicant: Watson Laboratories Inc.  
Agent for Applicant (if applicable):

Date of Application: December 12, 2007

Date of Receipt: December 13, 2007

Date clock started after UN:

Date of Filing Meeting: January 23, 2008

Filing Date: February 11, 2008

Action Goal Date (optional):

User Fee Goal Date: 10/13/08

Indication(s) requested: Benign Prostatic Hyperplasia

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)

Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.)  
Other (orphan, OTC, etc.) None

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, 5 Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**  
*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO   
 If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 56,605 silodosin
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
 If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) February 10, 2005 NO   
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) July 23, 2007 NO   
 If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO



ASSIGNED REVIEWERS (including those not present at filing meeting):

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Olivia Easley
Secondary Medical:	George Benson
Statistical:	Mahboob Sobhan
Pharmacology:	Laurie McLeod-Flynn
Statistical Pharmacology:	
Chemistry:	Yichun Sun
Environmental Assessment (if needed):	
Biopharmaceutical:	Doanh Tran
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Tavarez-Pagan
OPS:	
Regulatory Project Management:	Olga Salis
Other Consults:	
DDMAC	Lisa Hubbard
OSE	Cherye Milburn

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE   
 • Clinical site audit(s) needed? YES  NO   
 If no, explain:  
 • Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO   
 • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

• GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

• Establishment(s) ready for inspection? YES  NO

• Sterile product? YES  NO

If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS DISCUSSED**

1. Ensure each member of the Review Team has seen the new GRMP calculator with agreed dates.
2. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
3. Convey document filing issues/no filing issues to applicant by Day 74.

**AGREEMENTS REACHED**

1. Consults will be sent to DDMAC, DSI, OSE, DMETS and to the SEALD Team. All consulting groups have agreed to complete their reviews by April 1, 2008.
2. The Review Team will have all filing checklist in DFS along with review memos no later than February 11, 2008.
3. All primary reviews will be complete by August 6, 2008.

Olga Salis  
Regulatory Project Manager

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/s/

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Olga Salis  
2/7/2008 08:10:25 AM  
CSO

Olga Salis  
2/7/2008 08:11:13 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-206

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: silodosin capsules, 4mg and 8mg

Date of Application: December 12, 2007

Date of Receipt: December 13, 2007

Our Reference Number: NDA 22-206

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 11, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited 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 Reproductive and Urologic Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph., M.P.A.  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Products Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Margaret Kober  
12/19/2007 04:13:21 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 56,605

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for silodosin (KMD-3213).

We also refer to the meeting between representatives of your firm and the FDA on July 23, 2007. The purpose of the meeting was to gain agreement with FDA on the adequacy of the proposed NDA submission.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Medical Team Leader  
Division of Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 23, 2006  
**TIME:** 1:00PM to 2:30PM  
**LOCATION:** Room 1313  
**APPLICATION:** 56,605  
**DRUG NAME:** silodosin (KMD-3213)  
**TYPE OF MEETING:** Type B: Pre-NDA

**MEETING CHAIR:** George Benson, M.D.

**MEETING RECORDER:** Olga Salis

### **FDA ATTENDEES:**

Mark Hirsch, M.D. Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)

George Benson, M.D., Medical Team Leader, DRUP

Guodong Fang, M.D., Medical Officer, DRUP

Laurie, McLeod-Flynn, Ph.D., Pharmacologist, DRUP

Mahboob Sobhan, Ph.D., Lead Statistician, Division of Biometrics (DB III)

Doanh Tran, R.Ph., Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology

Olga Salis, Regulatory Health Project Manager, DRUP

### **EXTERNAL CONSTITUENT ATTENDEES:**

Kevin Barber, Ph.D., R.A.C., P.M.P., Executive Director, Regulatory Affairs

Paul G. Long, R.Ph., M.B.A., Associate Director, Biomedical Regulatory Affairs

Charles Ebert, Ph.D., Senior Vice President, Research and Development

Gary Hoel, R.Ph., Ph.D., Executive Director, Clinical Research

Lawrence Hill, Pharm.D., Director, Clinical Research

Weining Volinn, M.S., Associate Director, Biostatistics

Heather Thomas, Ph.D., Director, Biostatistics

\_\_\_\_\_ Regulatory Consultant

### **BACKGROUND:**

IND 56,605 was submitted on August 13, 1998, to study silodosin (KMD-3213) for the indication of treatment of the signs and symptoms of benign prostatic hyperplasia. On February 10, 2005, the Division and Watson held an End-of-Phase 2 meeting in which agreement was reached on the Phase 3 development program. On April 30, 2007, Watson requested a Type B Pre-NDA meeting. Meeting Packages were received on June 17, 2007. After reviewing the meeting packages, preliminary comments were faxed to the Sponsor on July 19, 2007.

### **MEETING OBJECTIVES:**

- To discuss Phase 3 efficacy and safety studies of silodosin prior to filing of the NDA.
- To address nonclinical items.
- To discuss clinical pharmacology and administrative items pertinent to the submission of the application.

## **DISCUSSION POINTS:**

The sponsor acknowledged receipt of the preliminary comments which the Division faxed on July 19, 2007. The responses in that document were used to guide the discussion.

## **QUESTIONS AND RESPONSES:**

### **PHARMACOLOGY / TOXICOLOGY**

1. Watson believes the nonclinical pharmacology/toxicology studies that will be submitted with the NDA are sufficient to support the filing of the NDA, and that no further studies are necessary for the Division's review of the nonclinical portion of the NDA. Does the Division agree?

*Division's Response: Yes. No further nonclinical studies are anticipated to be necessary to support filing.*

**Discussion: The sponsor had no comments or questions.**

### **CLINICAL PHARMACOLOGY**

2. Does the Division agree that the clinical pharmacology studies planned and completed are adequate to characterize the performance of the dosage form and strengths in support of the filing of an NDA?

*Division's Response: Based on your outline, it appears that you have generated sufficient data to support submission of an NDA from a Clinical Pharmacology perspective. We have the following comments and requests for information for the Clinical Pharmacology section of your NDA. Please be aware that comments a and b are potential filing issues.*

- a. *Confirm the Division's understanding that drug products used in Phase 1 pharmacokinetic (PK) studies were manufactured by Kissei Pharmaceuticals and at different site(s) than the Phase 3 and to-be-marketed products. This type of change in manufacturing site is considered to be a Level 3 change and requires bridging by a multi-point dissolution profile comparison (refer to Guidance for Industry: Immediate Release Solid Oral Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, in vitro Dissolution Testing, and in vivo Bioequivalence Documentation for additional information). Therefore, if the data from Phase 1 studies were generated using product manufactured at different sites from the to-be-marketed product, then you should conduct in vitro dissolution profile comparisons to ensure that the products are similar. Additionally, other significant changes in formulation or manufacturing may need to be bridged. Provide in the NDA a table of all clinical studies and the corresponding formulation(s) used in each study.*

**Discussion: The sponsor stated that six phase 1 studies were conducted using the same formulation and manufacturing site that was used in phase 3 trials. The studies are SI05008, SI05010, SI05014, SI06002, SI06004, and SI06008. According to the sponsor, all of these 6 studies used the 8mg dosage strength except for the hepatic impairment study, which also used 4mg. The sponsor raised a concern about the potential limited PK information on the 4mg dose. Other studies used prior products(s) manufactured by Kissei**

Pharmaceuticals. Sponsor indicated that they have historical dissolution data from products manufactured by Kissei Pharmaceuticals, but these were not identical batches to the ones used in phase 1 studies. Direct bridging between the current product and older products manufactured by Kissei Pharmaceuticals is not possible because the older products are no longer available.

The Division recommended that the sponsor submit a report before NDA submission detailing the formulation and manufacturing changes, any direct and indirect bridging of the formulations, and a table outlining the clinical studies and the associated formulation. The Division will review and provide comments. The sponsor agreed to submit the report.

- b. *Inform the Division whether any clinical study in support of this NDA was conducted in part by \_\_\_\_\_ sites between the period of January, 2000, and December, 2004.*

b(4)

**Discussion:** The sponsor stated that none of the studies was conducted by \_\_\_\_\_

b(4)

- c. *We acknowledge that you are conducting a study on the induction potential of silodosin and its major metabolites on the in vitro metabolic activities of CYP3A4 and CYP1A2. If the results show an induction potential, additional in vitro and in vivo studies may be necessary.*

**Discussion:** The sponsor acknowledged the Division's comment.

- d. *Provide a summary table of PK parameters obtained in all studies. The PK parameters should include AUC,  $C_{max}$ ,  $T_{max}$ ,  $t_{1/2}$  for silodosin and KMD-3213G. Provide the data as mean  $\pm$  standard deviation or median and range.*

**Discussion:** The sponsor agreed.

- e. *Include a discussion of silodosin dose proportionality, PK linearity, time to reach steady state, and drug accumulation in your NDA. Additionally, include in the Human Pharmacokinetics section a discussion on the relative receptor binding affinity of silodosin and its known metabolites with cross reference to the relevant preclinical study reports.*

**Discussion:** The sponsor agreed.

- f. *During NDA review, we may request electronic data files containing the raw and calculated PK parameters for some PK studies.*

**Discussion:** The sponsor stated that the NDA will include electronic datasets for all studies conducted in the US. Other studies conducted by Kissei are in paper format, which will include the raw PK data, and electronic datasets can be requested from Kissei.

3. During the teleconference on March 29, 2007, the Division recommended that Watson include a 4 mg dose of silodosin for \_\_\_\_\_ Does the Division agree in principle to the proposed wording in the Target Product Profile (TPP) for use of a 4 mg silodosin dose \_\_\_\_\_

b(4)

Division's Response: We agree in principle that a lower dose of 4 mg could be useful ———  
——— However, the determination of whether the 4 mg dose would be appropriate for  
—————  
————— will be determined during NDA review.

b(4)

**Discussion:** The sponsor agreed.

**CLINICAL**

4. Does the Division agree that the Phase 3 clinical studies demonstrate adequate efficacy to support the filing of an NDA for the proposed indication?

Division's Response: The summarized efficacy data from the two, U.S., Phase 3 studies appears adequate to support an NDA for the proposed submission. The filing decision is made after the NDA has been submitted.

**Discussion:** The sponsor had no comments or questions.

5. Does the Division agree that the Phase 3 clinical studies demonstrate adequate safety to support the filing of an NDA for the proposed indication?

Division's Response: The number of patients exposed and the duration of exposure appear to be adequate to assess safety of silodosin for the proposed indication. Again, the filing decision is made following NDA submission.

**Discussion:** The sponsor had no comments or questions.

6. Does the Division agree that the clinical database is of adequate size to support an approval of the NDA for the proposed indication?

Division's Response: The clinical database appears to be adequate to assess efficacy and safety, assuming that no additional safety concerns are identified during the review.

**Discussion:** The sponsor had no comments or questions.

7. Per 21 CFR 314.50(f)(2), Watson will submit case report forms (CRFs) for each patient in the U.S. Phase 2 and 3 studies who died or discontinued due to an adverse event, as well as CRFs for patients who experience Serious Adverse Events (SAEs). Does the Division agree with this proposal?

Division's Response: Yes.

**Discussion:** The sponsor had no comments or questions.

**Additional Clinical Comments from the Division:**

1. Following a preliminary review of your submitted Target Product Profile, we offer the following comments:

a. It does not appear that the submitted data will be sufficient to support the proposed statement

\_\_\_\_\_  
\_\_\_\_\_. Such a claim would require compelling evidence from adequately designed studies.

b(4)

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b. Claims of \_\_\_\_\_ are generally not acceptable for labeling.

b(4)

**Discussion:** The sponsor acknowledged the Division's comment.

c. In section 14, claims \_\_\_\_\_ may not be supported.

b(4)

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

2. The efficacy data for the 2 Phase 3 trials should be presented in the NDA by individual study.

**Discussion:** The sponsor will provide individual study data in the NDA and for the draft labeling.

**STATISTICS**

8. The clinical data sets will be submitted in Version 5 SAS transfer format and will not be provided in CDISC format. Is this plan acceptable to the Division?

Division's Response: Yes, SAS transport files are acceptable.

**Discussion:** The sponsor had no comments or questions.

9. Watson proposes not to submit the statistical analysis programs for the clinical studies, ISE, or ISS with the NDA. The analysis programs can be provided upon request. Is this proposal acceptable?

Division's Response: Yes.

**Discussion:** The sponsor had no comments or questions.

10. During the End-of-Phase 2 meeting, the Division affirmed that Watson will submit the safety results from the Japanese clinical studies previously conducted by Kissei as electronic datasets without integration of these safety data. In addition to these Japanese studies, Watson anticipates that safety results from a European Phase 3 study being conducted by another company, Recordati, may be available end of year 2007. If these results become available in final form prior to submission of the NDA, Watson likewise intends to submit a summary of these safety data in the same format (i.e., non-integrated) as the Japanese data. Does the Division agree with this proposal?

Division's Response: The safety data from the Japanese and European studies should be submitted as either final study reports, or as abbreviated or interim clinical study reports, if those studies are still ongoing at the time of NDA submission.

**Discussion:** The sponsor informed the Division that the reports of Japanese studies are available and will be included in the initial NDA submission. However, the sponsor stated that it is not clear whether the European safety data will be accessible to the sponsor prior to the planned submission date of December, 2007, and asked if the Division would accept the European safety data as part of the 120-Day Update.

The Division responded that submitting the European safety data in the 120-Day Update would be acceptable. However, the Division emphasized that all interim safety data that are available must be submitted. The Division requested that the sponsor submit a brief plan for the specific cut-off dates for inclusion of available European safety data in the initial NDA (if at all feasible) and in the 120-Day Update.

The sponsor agreed.

#### ADMINISTRATIVE AND REGULATORY

11. Watson intends to file the NDA for silodosin as an electronic CTD, using \_\_\_\_\_ as the third party vendor to compile the submission. A separate meeting has been requested for CMC items for filing; however, since the entire application will be electronic and in CTD format, Watson intends this discussion to cover the application as a whole.
- a) Does the division agree with Watson's plan to submit an eCTD?
  - b) \_\_\_\_\_ as the third party vendor, has filed numerous eCTDs to FDA in the past. Will Watson be required to submit a demonstration CD before filing the actual application?

Division's Response:

- a. Your plan to submit the application in eCTD format is acceptable.

b(4)

b(4)

b. — has successfully completed the pilot application process. If they are preparing your submission, you are not required to submit a pilot application.

b(4)

12. Watson will submit the data from the QTc study to the ECG Warehouse and will cross-reference the ECG Warehouse in the NDA. Is this acceptable to the Division?

*Division's Response:* The ECG waveforms should be submitted to the ECG warehouse. Yes, it is acceptable to cross-reference the ECG warehouse in the NDA.

**Discussion:** The sponsor had no comments or questions.

13. In the End-of-Phase 2 meeting with the Division, Watson requested a waiver of pediatric studies. At that time, the Division stated that pediatric studies can be —→ . Watson would like to again request that under the Pediatric Research Equity Act (PREA) studies for BPH in pediatric patients be waived. Does the Division agree that silodosin qualifies for a waiver of pediatric studies for BPH?

b(4)

*Division's Response:* We continue to believe that a pediatric ————— should be granted.

b(4)

**Discussion:** The sponsor asked for clarification from the Division regarding their position that a ————— t a waiver should be granted, pointing out that BPH does not exist in pediatric patients.

b(4)

The Division agreed that BPH is not seen in children, but stated that silodosin may be used for other reasons in pediatric populations.

The sponsor acknowledged the comments from the Division.

14. Does the Division have any view at this time as to whether an advisory committee meeting may be requested during the NDA review?

*Division's Response:* We currently have no plans for an advisory committee during the NDA review.

**Discussion:** The sponsor had no comments or questions.

**Additional discussion Items:**

The sponsor inquired about the status of the review of the proposed trade name submitted to the Division in September, 2006.

The Division has recently received the consultation from the Division of Medication Errors and Technical Support (DMET's) and will inform the sponsor by letter as to the current status of the proposed trade name. The trade name will also need to be re-reviewed within 90 days of NDA action date.

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/s/

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George Benson  
8/13/2007 12:09:20 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 56,605

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for silodosin (KMD-3213).

We also refer to the teleconference between representatives of your firm and the FDA on March 29, 2007. The purpose of the meeting was to discuss the proposed QT study in your submission dated February 9, 2007, received February 12, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Medical Team Leader  
Division of Reproductive and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** March 29, 2007  
**TIME:** 2:00 – 3:00 PM  
**LOCATION:** White Oak, 5201 (Teleconference)  
**APPLICATION:** IND 56,605  
**DRUG NAME:** silodosin  
**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** George Benson, M.D.

**MEETING RECORDER:** Jennifer Mercier

### **FDA ATTENDEES:**

Mark Hirsch, M.D. – Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)

George Benson, M.D. – Medical Team Leader, DRUP

Guodong Fang, M.D. – Medical Officer, DRUP

Myong Jin Kim, Pharm.D. – Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)

Doanh Tran, R.Ph., Ph.D. – Clinical Pharmacology Reviewer, OCP

Jennifer Mercier – Chief, Project Management Staff, DRUP

### **EXTERNAL CONSTITUENT ATTENDEES:**

Kevin Barber, Ph.D., R.A.C., PMP – Executive Director, Regulatory Affairs

Paul G. Long, R.Ph., MBA – Associate Director, Biomedical Regulatory Affairs

Charles Ebert, Ph.D. – Senior Vice President, Research and Development

Gary Hoel, R.Ph., Ph.D. – Executive Director, Clinical Research

Weining Volinn, M.S. – Associate Director, Statistics

\_\_\_\_\_ – Regulatory Consultant

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### **BACKGROUND:**

The sponsor submitted a “thorough QT” (TQT) protocol for the Division’s review on September 22, 2006, serial 094. On November 15, 2006, the Division and sponsor had a teleconference to discuss safety of the sponsor’s proposed 48 mg suprathapeutic dose. During that teleconference, the Division expressed concern regarding the dose being too high. Also during that teleconference, the sponsor proposed to conduct a drug-drug interaction study with 8 mg silodosin and 400 mg ketoconazole prior to finalizing the protocol for the thorough QT study. Subsequently, summary results from the ketoconazole interaction study were submitted along with a revised QT protocol. The suprathapeutic dose proposed for the TQT study was revised to 32mg.

### **MEETING OBJECTIVES:**

To discuss the suprathapeutic dose of the silodosin to be used in the “thorough QT” study and to provide any additional comments and recommendations about the TQT protocol.

## DISCUSSION POINTS:

- The Division expressed concern with the suprathapeutic dose of 32 mg silodosin that the Sponsor had proposed in the February 9, 2007 submission for the "thorough QT" study. The Division expressed this concern based upon heart rate and blood pressure data the Sponsor had submitted at the Division's request.
- Based on the safety concern (hypotension) at high doses, and the 3.7-fold increase in silodosin Cmax when taken with ketoconazole, the Division recommended the sponsor consider pursuing a dose lower than 8mg for

- The Division also stated that a suprathapeutic dose of 24mg in the TQT study was expected to be safer than the 32mg dose. However, this safety concern did not rise to level of a Clinical Hold since the subjects would be adequately monitored and well informed of potential risks. The Division also stated that a 24mg dose would likely provide systemic silodosin exposures higher than those expected in patients taking ketoconazole and silodosin 4mg.
- The Sponsor was concerned about developing the 4 mg dose of silodosin at this stage because of the possibility of not having enough stability data at the time of NDA submission, but was receptive to the idea and would investigate further.
- The sponsor further clarified their rationale for selection of the 32 mg dose for the "thorough QT" study. The 32mg dose was selected because it was believed to be reasonably safe in the context of a well-monitored TQT study, and it was expected that the 32mg dose would provide systemic exposures that were higher than exposures seen in subjects taking silodosin 8mg and ketoconazole. They acknowledged the potential safety risks at 32mg, but believed that the study was still reasonably safe, and that the potential benefits of the study outweighed the risks.
- The sponsor acknowledged the Division's concern with the 32mg dose and advice to consider a lower suprathapeutic dose in the TQT study, and the Division's proposal to The Sponsor will look into the feasibility of modifying the TQT protocol to change the suprathapeutic dose selection to the 24 mg silodosin.
- The Division requested the sponsor to submit the informed consent being used for the TQT study and the Sponsor agreed to provide it. The Sponsor informed the Division that the current informed consent stated that a maximum dose of 32 mg dose was to be used, when in fact, a change to the 24 mg silodosin dose would be considered.
- The Division provided several additional comments in regard to specific procedures for the TQT study. The Division committed to sending all remaining TQT study protocol comments promptly.

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## ACTION ITEMS:

- Sending sponsor meeting minutes within 30 days.
- The sponsor will fax the informed consent to the Division.
- The sponsor will investigate the feasibility of modifying the suprathapeutic dose in the "thorough QT" study.
- The sponsor will investigate the feasibility of developing a 4 mg silodosin dose.
- The Division will promptly convey all remaining TQT study protocol comments.

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George Benson  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 56,605

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., M.B.A.  
Associate Director, Regulatory Affairs  
577 Chipeta Way  
Salt Lake City, UT 84108

Dear Mr. Long:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for silodosin (KMD-3213).

We also refer to the meeting between representatives of your firm and the FDA on October 13, 2006. The purpose of the meeting was to discuss bioequivalence of the 8 mg capsule, a matrixed stability protocol, and \_\_\_\_\_ for the drug substance. b(4)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 796-0928.

Sincerely,

*{See appended electronic signature page}*

Ameeta Parekh, Ph.D.  
Clinical Pharmacology Team Leader  
Office of Clinical Pharmacology  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 13, 2006  
**TIME:** 11:00 – 11:15:00 a.m.  
**LOCATION:** Teleconference  
**APPLICATION:** IND 56,605  
**DRUG NAME:** silodosin (KMD-3213)  
**TYPE OF MEETING:** Type C (Guidance)

**MEETING CHAIR:** Stephan Ortiz, R.Ph., Ph.D.

**MEETING RECORDER:** Martin Kaufman, D.P.M., M.B.A.

### FDA PARTICIPANTS:

Stephan Ortiz, R.Ph., Ph.D., Clinical Pharmacologist, Office of Clinical Pharmacology (OCP)  
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)  
Guodong Fang, M.D., Medical Officer, DRUP  
Chong Kim, M.D., Ph.D., Medical Officer, DRUP  
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUP

### EXTERNAL CONSTITUENT PARTICIPANTS:

Kevin Barber, Ph.D., R.A.C., P.M.P., Executive Director, Regulatory Affairs  
Cherri Petrie, R.A.C., Director, Regulatory Affairs C.M.C.  
Paul G. Long, R.Ph., M.B.A., Associate Director, Regulatory Affairs Biomedical  
Mamun Khan, Ph.D., Executive Director, Research and Development Analytical Services

### BACKGROUND:

IND 56,605 was submitted on August 13, 1998, to study silodosin (KMD-3213) for the indication of treatment of the signs and symptoms of benign prostatic hyperplasia. Currently, the sponsor is conducting phase 3 clinical studies in which two 4 mg capsules are administered once daily. To facilitate easier administration and to improve patient compliance, the sponsor is developing a new 8 mg capsule formulation for once a day dosing. The sponsor's meeting request and meeting package were received by the Division on August 11, 2006. A Type C meeting was granted and scheduled for October 13, 2006. After reviewing the meeting package, preliminary comments were faxed to the sponsor on October 10, 2006.

### MEETING OBJECTIVES:

To discuss and obtain the Division's input concerning:

1. The biopharmaceutical aspects of the 8 mg capsule.
2. The acceptability of a proposal for a matrixed stability protocol.
3.                      for the drug substance.

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### DISCUSSION POINTS:

The sponsor acknowledged receipt of the preliminary comments which the Division faxed on October 10, 2006. The responses in that document were used to guide the discussion.

Sponsor's Questions

**Clinical Pharmacology**

Question 1:

*Does the Division agree that the proposed in-vitro comparison is adequate, and that no in-vivo bioequivalence study is required to support approval of the 8-mg capsule in the NDA?*

**Response:** Yes. The Division agrees that the proposed in-vitro comparison is adequate, and that no in-vivo bioequivalence study is required to support approval of the 8-mg capsule in the NDA.

Question 2:

*Please confirm that the in-vitro study adequately addresses the* \_\_\_\_\_

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**CMC**

Question 1:

*Does the Division agree that the pre-approval testing conducted under the proposed matrixing design is appropriate to generate a package of stability data to support:*

- a. *The establishment of product shelf-life and specifications for the 4-mg and 8-mg silodosin capsules?*
- b. *The continued use of a matrixed approach to stability testing across the proposed container/closure configurations post-approval?*

**Response:** Yes, the matrixing plan is adequate. Confirm that the same plan will be used for the 4 mg capsules, and that 12 months of stability data will be submitted in the NDA.

Question 2:

*Does the Division agree that the proposed dissolution medium, 0.1 N HCl, is appropriate for NDA filing for 4 mg and 8 mg silodosin capsules?*

**Response:** Yes, 0.1 N HCl is an appropriate dissolution media for both the 4 mg and 8 mg capsules.

**ACTION ITEM:**

- The Division will send official meeting minutes to the sponsor within 30 days of the date of this meeting.

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Ameeta Parekh  
10/24/2006 02:29:25 PM



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE III

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** July 28, 2005

<b>To:</b> Paul Long., R.Ph.	<b>From:</b> Martin Kaufman, D.P.M., M.B.A.
<b>Company:</b> Watson Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
<b>Fax number:</b> 801 588-6232	<b>Fax number:</b> 301-827-4267
<b>Phone number:</b> 801 588-6224	<b>Phone number:</b> 301-827-4234
<b>Subject:</b> IND 56,605	

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:**       YES       NO

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Attachment

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** July 22, 2005  
**TIME:** 1:00 – 2:00 pm  
**LOCATION:** Teleconference  
**APPLICATION:** IND 56,605  
**DRUG NAME:** silodosin (KMD-3213)  
**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** George Benson, M.D.

**MEETING RECORDER:** Martin Kaufman, D.P.M.

**FDA PARTICIPANTS:**

George Benson, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580  
Guodong Fang, M.D., Medical Officer, DRUDP, HFD-580  
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

**EXTERNAL CONSTITUENT PARTICIPANTS:**

Dorothy A. Frank, M.S., R.A.C., Executive Director, Regulatory Affairs  
Paul G. Long, R.Ph., M.B.A., Manager, Regulatory Affairs  
Gary Hoel, R.Ph., Ph.D., Executive Director, Clinical Research  
Lawrence Hill, Pharm.D., Senior Principal Scientist, Clinical Research  
Heather Thomas, M.S., Ph.D., Associate Director, Biostatistics  
Charles Ebert, Ph.D., Senior Vice President, Research and Development  
Gregory Parry, Project Manager  
William Good, Ph.D., Vice President of Development  
Regulatory Consultant

**b(4)****BACKGROUND:**

On June 30, 2005, the Division sent the sponsor a letter with the following comments and recommendations regarding monitoring for prolactin and thyroid adverse events in silodosin phase 3 trials:

1. The Division believes that serum prolactin levels should be determined in a subgroup of patients in both the drug and placebo groups at baseline and at the end of the 12 week phase 3 trials. In addition, all patients should have a breast examination included in the baseline and end-of-study physical examinations.
2. Measurement of free T4, total T3, and TSH should be performed at baseline and at the end of the 12 week study period in all drug/placebo patients in phase 3 trials. All patients should have a neck/thyroid examination included in the baseline and end-of-study physical examinations. In addition, free T4, total T3, and TSH as well as neck physical examinations should be performed on all patients at the end of the one year open label extension study. In order to interpret these results, an age matched untreated control group should be included. A consulting endocrinologist from the Division of Metabolic Drug Products has recommended obtaining thyroid ultrasound examinations in patients at baseline and at end of study. Please respond to this recommendation in a submission to the Division.

The sponsor responded to that letter in a submission (serial 063) dated July 18, 2005. This teleconference was requested by the sponsor in order to discuss proposals included in that submission.

**MEETING OBJECTIVES:**

- To discuss the sponsor's proposals for serum prolactin and thyroid monitoring.

**DISCUSSION POINTS:**

- The sponsor's proposal to amend ongoing protocols SI04009 and SI04010 to include prolactin assays and breast exams is acceptable to the Division. The Division understands that approximately 400 patients (200 silodosin and 200 placebo) will have baseline and end-of-study prolactin levels and breast examinations. All patients will have an end-of-study assessment.
- The sponsor's proposal to amend protocols SI04009 and SI04010 to include a free T4 assay at visit 1 and at the end of the study is acceptable to the Division.
- The sponsor's proposal to amend protocols SI04009, SI04010, and SI04011 to include a thyroid examination is acceptable to the Division.
- The sponsor does not believe that evaluating an age-matched untreated control group would be beneficial in interpreting the results of thyroid hormone levels and thyroid examinations at the end of the one year open label extension study. The sponsor will submit the reasons for this conclusion for the Division's consideration.
- The sponsor does not believe that the performance of baseline and end-of-study thyroid ultrasounds are warranted and will provide the reasons for this conclusion for the Division's consideration.

**ACTION ITEMS:**

- The sponsor will provide additional rationale for its position concerning the addition of an age matched control group and inclusion of thyroid ultrasound examinations.

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CSO

George Benson  
7/26/05 03:09:52 PM  
MEDICAL OFFICER

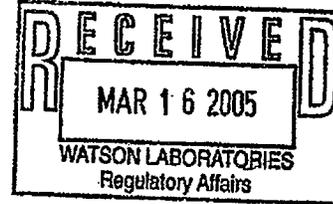


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 56,605

Watson Laboratories, Inc.  
Attention: Paul Long, R.Ph., Manager, Regulatory  
Liaison, U.S. Proprietary Products  
577 Chipeta Way  
Salt Lake City, UT 84108



Dear Mr. Long:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for silodosin (KMD-3213).

We also refer to the meeting between representatives of your firm and the FDA on February 10, 2005. The purpose of the meeting was to discuss Phase 3 study designs, safety database requirements, and preclinical carcinogenicity data.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 827-4234.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Medical Team Leader  
Division of Reproductive and Urologic Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** February 10, 2005  
**TIME:** 10:00 – 11:30 a.m.  
**LOCATION:** Conference Room 'L' Parklawn Building  
**APPLICATION:** IND 56,605  
**DRUG NAME:** silodosin (KMD-3213)  
**TYPE OF MEETING:** Type B, End of Phase 2

**MEETING CHAIR:** George Benson, M.D.

**MEETING RECORDER:** Martin Kaufman, D.P.M., M.B.A.

**FDA ATTENDEES:**

Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580  
George Benson, M.D., Medical Team Leader, DRUDP, HFD-580  
Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUDP, HFD-580  
Guodong Fang, M.D., Medical Officer, DRUDP, HFD-580  
Laurie McLeod-Flynn, Ph.D., Pharmacologist, DRUDP, HFD-580  
Stephan Ortiz, R.Ph., Ph.D., Clinical Pharmacologist, Division of Pharmaceutical Evaluation II (DPE II), HFD-870  
Dhruba Chatterjee, Ph.D., Clinical Pharmacologist, DPE II, HFD-870  
Mahboob Sobhan, Ph.D., Statistician, Division of Biometrics II (DB II), HFD-715  
Anthony Parola, Ph.D., Pharmacologist, DRUDP, HFD-580  
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

**EXTERNAL CONSTITUENT ATTENDEES:**

Dorothy A. Frank, M.S., R.A.C., Executive Director, Regulatory, Watson Laboratories, Inc.  
Paul G. Long, R.Ph., M.B.A., Manager Regulatory, Watson Laboratories, Inc.  
Gary Hoel, R.Ph., Ph.D., Executive Director, Clinical Research, Watson Laboratories, Inc.  
Lawrence Hill, Pharm.D., Senior Principal Scientist, Clinical Research, Watson Laboratories, Inc.  
Heather Thomas, M.S., Ph.D., Associate Director, Biostatistics, Watson Laboratories, Inc.  
Charles Ebert, Ph.D., Senior Vice President, Research and Development, Watson Laboratories, Inc.

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\_\_\_\_\_  
Clinical Consultant,  
Regulatory Consultant,  
\_\_\_\_\_, Toxicology Consultant, \_\_\_\_\_

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**BACKGROUND:**

Silodosin is a new chemical entity developed by Kissei Pharmaceuticals, Inc. It is an  $\alpha$ -adrenergic receptor antagonist with a proposed indication for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). IND 56,605 was opened in September, 1998, by Watson Laboratories, Inc., which owns the North American licensing rights to the compound. Since 1996, approximately 1,928 patients have participated in fourteen Phase I and seven Phase

2 and Phase 3 studies in Japan, the United States, and the United Kingdom. The sponsor plans to start enrolling patients in its Phase 3 clinical trials in April, 2005. This meeting was requested by the sponsor in order to discuss the design of the Phase 3 trials and gain agreement with the Division on the adequacy of its development program.

**MEETING OBJECTIVES:**

- To address the Division's March 4, 2004, letter requesting mechanistic explanations for tumors and the quantification of human metabolites.
- To clarify that no additional preclinical issues are outstanding, and that the preclinical data appear to support the Phase 3 study and NDA filing.
- To provide the Division with Watson's Phase 3 development plan for review and comment.
- To confirm that the proposed Phase 3 clinical protocols will support an approval for the indication of the treatment of signs and symptoms of BPH.

**DISCUSSION POINTS:**

**Pharmacology/Toxicology:**

**Question 1:** *Does the micronucleus Study 50048 submitted in S-024 satisfy the Division's request for additional micronucleus data?*

**Answer:** Yes, the micronucleus study number 50048 satisfies the Division's request for additional micronucleus data.

**Question 2:** *Kissei submitted a 12 month dog study to the IND in S-007 with 4/sex/group. An additional 4 week dog study containing liver and kidney concentration data was submitted in S-028. Do these studies satisfy the Division's initial requests made during the pre-IND meeting for the 12 month dog study?*

**Answer:** Yes, the 52-week dog study and the 4-week supplemental pharmacokinetic study are sufficient.

**Question 3:** *Do the mechanistic explanations on the cause of breast and thyroid tumors in rodents address the Division's request to demonstrate that silodosin is not a risk to humans at the expected clinical exposure?*

**Answer:** No. The mechanistic explanations from animal studies are sufficient. However, complementary evidence that the hormonal mechanisms theorized to be responsible for breast and thyroid tumors in animals (e.g. high prolactin levels) are not present at clinical dose levels in humans should be submitted as well. Evidence that thyroid hormones (TSH, T3, T4) are not directly affected in clinical subjects should also be submitted.

**Question 4:** *Will the quantification of human metabolites from separate studies meet FDA's needs for calculating the no-effect level?*

**Answer:** No. For the purpose of calculating no effect levels of parent drug and metabolites in carcinogenicity studies, the average steady state chronic clinical exposures (AUCs) should be used as comparators. All major human metabolites should be represented in at least one carcinogenicity study at at least the average clinical exposure. The glucuronide conjugate, which is not represented in preclinical studies, does not show any indicators of genotoxicity, of precarcinogenic lesions in the subchronic study, or a structural concern for additional carcinogenicity; it, therefore, would not trigger an additional carcinogenicity assay.

**Sponsor's Response:** The sponsor intends to submit 8 mg PK data for all metabolites.

**Question 5:** *Watson believes that the toxicology of the glucuronide metabolite has been reasonably determined to support the Phase 3 studies and the NDA submission. Does the Division agree?*

**Answer:** No. It is not anticipated that additional studies of the glucuronide metabolite will be requested. However, other metabolites which represent greater than 10% of the total clinical exposure after chronic administration will trigger requests for further studies if they cannot be shown to be adequately covered in completed studies.

**Question 6:** *Watson believes a full set of toxicology studies have been completed to support the Phase 3 studies and the NDA submission. Does the Division agree?*

**Answer:** Yes. Comparative pharmacokinetics, as discussed in question number 4, and additional metabolite studies, if necessary, may be submitted concurrently with phase III.

**General comment:**

It is recommended that a segment III developmental study be submitted with the NDA.

**Clinical Pharmacology:**

**Question 1:** *Does the Division agree that the proposal for drug interaction information will support the proposed TPP and the NDA?*

**Answer:** The in vitro drug interaction studies suggest that silodosin in vivo has a low potential for causing interactions (inducing/inhibiting CYP450) with other drugs through cytochrome mediated metabolism. According to the meeting package, the  $C_{max}$  values used in estimating drug interaction potential were values obtained from multiple dose administration of 4 mg BID after 7 days. Since the anticipated dosing will be 8 mg QD, the calculations should be repeated with the estimated  $C_{max}$  obtained from 8 mg QD dosing in the fasted state (worst-case scenario).

**Discussion:** There was discussion as to whether the appropriate  $C_{max}$  was used in estimating the  $C_{max}/K_i$  value. The sponsor explained that when the calculations were repeated using the  $C_{max}$  obtained from 8 mg QD dosing, the  $C_{max}/K_i$  value was still below 0.2. The sponsor was asked to submit the new calculations.

**Question 2:** *It is believed that silodosin has low potential for causing interactions through cytochrome mediated metabolism and no clinical studies have been subsequently performed. Does the Division agree that the in vitro pharmacokinetic interactions data is sufficient for filing purposes?*

**Answer:** It is unclear from the submitted in vitro interaction studies appendix whether the sponsor has shown that no further in vivo studies are required.

**Question 3:** *Does the Division agree that the renal impairment study supports a*

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**Answer:** Labeling is not addressed until the completed NDA has been submitted to the Division.

**Additional comment:**

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**Question 4:** *Watson is planning to conduct a study of the use of silodosin in patients with moderate hepatic impairment. Does the Division have any comments on the current protocol outline for the study?*

**Answer:** No, but not enough detail regarding this trial is submitted.

**Question 5:** *Along with the proposed hepatic study, does the Division agree that the pharmacokinetic studies completed to date are adequate to characterize the performance of the dosage form in support of the NDA?*

**Answer:** The Agency recommends further pharmacokinetic studies to fully characterize the ADME of silodosin. Please see **Additional Comments** below. We recommend submitting the protocols to the Division for review prior to initiating the trial.

**Question 6:** *Watson is planning to conduct a QTc interaction study with silodosin. Does the Division have any comments on the current protocol outline for the study?*

**Answer:** The proposed supratherapeutic dose is 16 mg, or two times greater than the proposed therapeutic dose. When choosing a supratherapeutic dose, the sponsor should choose a dose that represents the "worst-case" scenario clinically. From the information presented, a two-fold increase in exposure does not appear to satisfy this criterion. It is recommended that the sponsor submit the full QTc study protocol to the Division for review prior to initiation of the study.

**Sponsor's Comment:** The sponsor will reevaluate and provide justification for the supratherapeutic dose.

**Additional Comments:**

- We recommend an in vitro induction study be performed.
- We recommend that the sponsor perform in vitro studies to determine the CYP450 enzymes involved in the metabolism of silodosin. The results of these studies may lead to recommendations regarding in vivo drug interaction studies.
- It is recommended that the sponsor submit the full QTc study protocol to the Division for review prior to initiation of the study.

**Discussion:** Studies which have already been performed that characterize the metabolic pathways of silodosin were discussed. The sponsor will provide a summary of the available studies.

**Clinical:**

**Question 1:** *Does the Division agree that the Phase 3 clinical study protocols are sufficient to demonstrate efficacy and support the proposed indication in an NDA?*

**Answer:** Yes. The general design of the two phase 3 studies described in the meeting package appears to be sufficient to support efficacy for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia."

**Additional Comment:** The Division recommends submitting the final phase 3 protocol(s) as a Special Protocol Assessment (SPA) for Division concurrence. Submission of a SPA is not, however, mandatory.

**Question 2:** *Does the Division agree that the study design (i.e. one treatment arm and one placebo arm) is sufficient to demonstrate efficacy and support the proposed indication?*

**Answer:** Based on the information presented in the meeting package, the Division does not currently agree with the single treatment arm of 8 mg. It is not clear whether 4 or 8 mg is the lowest effective dose. In addition, further efficacy and safety data on the 4 mg dose may be needed as this dose may be recommended in patients \_\_\_\_\_

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**Question 3:** *Does the Division agree that the patient population, as defined by the inclusion and exclusion criteria, is appropriate for the proposed indication?*

**Answer:** The Division recommends that the inclusion criteria for  $Q_{max}$  be 5 to 12 cc/sec. Otherwise the inclusion/exclusion criteria are acceptable.

**Additional Comment:** Maximum flow rate is a secondary endpoint; the primary endpoint is the IPSS.

**Question 4:** *Does the Division agree with Watson's proposal for safety monitoring in the proposed clinical trials?*

**Answer:** The Division recommends that thyroid function tests (T3, T4, and TSH) and serum prolactin levels also be monitored.

**Sponsor's Question:** What is the recommended frequency for thyroid function tests?

**Division' Response:** Our minimum recommendation is that thyroid function tests be done at baseline, end of study, and end of the open label study.

The sponsor presented a summary of prolactin determinations (see attachment). There was a discussion of the summary, and the sponsor agreed to submit the actual data.

**Question 5:** *Does the Division agree with the overall safety submission proposal and agree that Watson will have sufficient patient exposure for the NDA?*

**Answer:** In general, yes. If new safety concerns are identified, the numbers of patients studied may need to be increased.

**Question 6:** *Will the Division accept pivotal data from one or more Phase 3 studies conducted in India?*

**Answer:** Yes, provided that all data can be adequately audited.

**Question 7:** *Does the Division agree with the proposal for the manner in which the Japanese safety data will be provided?*

**Answer:** Yes.

**Additional Comment:** The data may be submitted electronically.

**Question 8:** *Watson is planning to conduct a QTc interaction study with silodosin. Does the Division have any comments on the current protocol outline for the study?*

**Answer:** The maximum dose of silodosin to be studied needs further discussion. The QT study protocol should be submitted to the Division for concurrence prior to its initiation. Please see Clinical Pharmacology comments above.

**Question 9:** *Does the Division agree that silodosin qualifies for a waiver of pediatric studies?*

**Answer:** — pediatric studies can be —

**Additional Comment:** \_\_\_\_\_

**b(4)**

**Question 10:** *Does the Division have any additional comments concerning the development plan?*

**Answer:** No.

**Biostatistics:**

**Question 1:** *Is the definition of the primary efficacy analysis population for the Phase 3 studies acceptable?*

**Answer:** We agree with the sponsor's definitions of the primary analysis population (modified intent-to-treat), but we do not understand how that differs from ITT as defined in section 11.2, page 157.

**Sponsor's Response:** The sponsor will provide details of the analysis with the ITT population as well.

**Question 2:** *Is the method of imputation, LOCF, for missing data acceptable for the Phase 3 efficacy endpoints?*

**Answer:** Generally, we do not suggest that LOCF should be the method of choice for imputing missing data without first checking the type of missing data pattern. Depending on the missing data pattern, other methods such as mixed model repeated measures (MMRM) method could also be explored.

**Question 3:** *Is the proposed statistical analysis model and level of significance,  $\alpha=0.05$ , for each efficacy endpoint in the Phase 3 studies acceptable?*

**Answer:** Yes, the statistical analysis model is acceptable.

**Question 4:** *Is the proposed statistical analysis plan for the remaining efficacy and safety parameters of the Phase 3 studies acceptable?*

**Answer:** Yes.

**ACTION ITEMS:**

- Meeting minutes to the sponsor within thirty days

**ATTACHMENTS/HANDOUTS:**

- Sponsor's slides

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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George Benson  
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Executive CAC

Date of Meeting: January 6, 2004

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Abby Jacobs, Ph.D., HFD-024, Member  
Terry Peters, D.V.M, HFD-520, Alternate Member  
Laurie McLeod-Flynn, Ph.D., Presenting Reviewer/Acting Team Leader

Author of Draft: Laurie McLeod-Flynn

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND # 56,605

Drug Name: KMD-3213

Sponsor: Kissei Pharma USA, Inc., Hackensack, NJ

#### Background:

KMD-3213 is an alpha-1 adrenoceptor antagonist being developed for benign prostatic hyperplasia. It was negative in bacterial reverse mutation assays, mammalian cell mutation assays, rat DNA repair assay, chromosomal aberration assay, and micronucleus test.

#### Male Mouse Carcinogenicity Study

This was a dietary two-year bioassay in male CD-1 (ICR) BR mice (50/group). The dosing groups were 0, 0, 20, 60, and 200/100 mg/kg/day, based on high dose AUC multiples greater than 25 times the average expected clinical exposure. Doses were reduced in the high dose group after week 26 due to excessive decreases in body weight gain in the high dose group. Thereafter, body weight gain was comparable among groups. No significant difference in survival among groups was observed.

No treatment related neoplasms were observed.

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#### Female Mouse Carcinogenicity Study

This was a dietary two-year bioassay in female CD-1 (ICR) BR mice (50/group). The dosing groups were 0, 0, 60, 150, and 400 mg/kg/day, based on high dose AUC multiples greater than 25 times the average expected clinical exposure. The high dose caused a lowered body weight gain, from approximately week 10 in the 400 mg/kg/day group compared with combined controls (-24% at week 102). The corresponding body weight gains for the 60 and 150 mg/kg/day groups were -5% and -14 %, respectively. No significant difference in survival among groups was observed.

In the sponsor's analysis, mammary adenocarcinoma, mammary adenoma, and combined adenoma plus carcinoma showed increasing trends ( $p < 0.001$ ). Pairwise comparisons were also statistically significant between the pooled controls and the high dose group.

The trend test for mammary adenoacanthoma was also significant ( $p < 0.001$ ), as was pairwise comparison of the pooled controls and high dose group ( $p < 0.001$ ).

An increased incidence of mammary atypical hyperplasia, lobular hyperplasia and squamous metaplasia was observed in the high and intermediate dose groups.

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MOUSE TUMOR FINDINGS:

	Females (mg/kg/day)				
	0	0	60	150	400
Mammary gland					
adenocarcinoma	4	2	2	7	12
adenoacanthoma	1	1	0	1	11
carcino-sarcoma	0	0	0	0	1
mammary adenoma	0	1	0	1	0

Background data in CD-1 female mice from studies conducted January 1992 to June 1999												
Female histor. data study	A	B	C	D	E	F	G	H	I	J	K	
Adenocarcinoma	2	0	1	2	2	1	3	2	0	3	1	
Adenoacanthoma	2	0	0	0	0	1	0	0	0	1	0	
Number of mammary exam.	56	56	60	50	50	56	50	50	47	60	69	

Rat Carcinogenicity Study

This was a dietary two-year bioassay in male and female — CD® (SD) IGS BR rats (60/group). The dose groups were 0, 0, 15, 50, and 150 mg/kg/day in males and 0, 0, 15, 80, and 250 mg/kg/day in females, based on high dose AUC multiples greater than 25 times the average expected clinical exposure. No significance differences among groups for body weight gain or survival were observed.

In the sponsor's analysis, the incidence of thyroid follicular cell adenomas was statistically significant in male rats receiving 150 mg/kg/day vs. pooled controls (Fisher's Exact Test  $p < 0.001$ ), as was the test for trend ( $p < 0.001$ ).

When benign and malignant thyroid follicular cell tumors in male rats were combined, there was a statistically significant trend ( $p < 0.001$ ). The pairwise comparison between pooled controls and the high dose group was also statistically significant ( $p < 0.001$ ).

In female rats receiving 250 mg/kg/day, the incidence of thyroid follicular cell adenoma was increased but was not statistically significant.

The incidence of follicular cell hypertrophy was statistically significant in all treated groups of male rats and in female rats receiving 250 mg/kg/day. The incidence in female rats administered 80 mg/kg/day also appeared to be increased, but was not statistically significant. Follicular cell hypertrophy showed an apparent increase in severity in both male and female rats.

The incidence of cystic follicular cell hyperplasia was statistically significant in male rats receiving 150 mg/kg/day and also appeared to be increased in the other dose groups. Cystic follicular cell hyperplasia showed an apparent increase in severity in male rats.

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RAT TUMOR FINDINGS:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	15	50	150	0	0	15	80	250
Thyroids (N)	60	60	60	60	59	59	60	60	59	60
follicular cell adenoma	1	0	1	4	12	1	0	2	2	4
follicular cell carcinoma	1	1	0	1	2	0	0	0	0	0

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	15	50	150	0	0	15	80	250
Thyroids (N)	60	60	60	60	59	59	60	60	59	60
follicular cell hypertrophy (total)	2	4	10*	11*	11**	1	0	1	3	14***
minimal	0	2	5	7	2	0	0	1	0	4
slight	2	2	5	4	9	1	0	0	3	10
cystic follic. cell hyperplasia (total)	0	1	4	3	5	2	0	0	0	2
minimal	0	0	3	0	0	1	0	0	0	1
slight	0	0	1	2	3	0	0	0	0	1
moderate	0	1	0	1	2	1	0	0	0	0

Background in $\sim$ : CD rats																		
Male histor. data study	A		B		C		D		E		F		G		H		I	
(D=decedent, T=terminal)	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T
Follicular cell adenoma	0	3	0	0	4	2	1	2	1	1	1	0	3	1	0	2	0	2
Follicular cell carcinoma	0	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0	0
# of thyroids examined	29	21	35	25	28	22	31	19	31	19	28	32	40	25	39	26	29	36

Female histor. data study																		
(D=decedent, T=terminal)	A		B		C		D		E		F		G		H		I	
(D=decedent, T=terminal)	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T	D	T
Follicular cell adenoma	1	1	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0
Follicular cell carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
# of thyroids examined	31	19	44	16	34	16	36	13	33	17	36	24	43	22	40	24	44	21

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Executive CAC Recommendations and Conclusions:

Rats:

- \* The Committee agreed that the rat study was adequate.
- \* The committee concurred that the thyroid follicular cell adenomas in male rats were drug related. Although the incidence of follicular cell adenomas in female rats was increased, the incidences in dosed groups were not statistically significant and thus not clearly related to the drug. However, the committee noted that the increased incidence and severity, although minimal to slight, of thyroid follicular cell hypertrophy in the female rats, as well as in the male rats, suggests that the thyroid of females is also a potential organ for toxicity of the drug.

Mice:

- \* The Committee agreed that the mouse carcinogenicity studies were adequate.

Female mice:

- \* The Committee concurred that the mammary gland adenoacanthomas were drug related. The committee also concurred that the mammary gland adenocarcinomas, and adenomas or carcinomas, were drug related.

Male mice:

- \* The committee concurred that there were no drug-related neoplasms in male mice.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, HFD-580  
/Laurie McLeod-Flynn, HFD-580  
/Dale Cutright, HFD-580  
/ASeifried, HFD-024

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/s/

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Abby Jacobs

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