APPLICATION NUMBER:

22-030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DRAFT 10/14/08

EXCLUSIVITY SUMMARY

NDA # 22-030 SUPPL # HFD #

Trade Name Toviaz

Generic Name Fesoterodine fumarate

Applicant Name Pfizer

Approval Date, If Known October 31, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1 !
 !
 IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !
 IND # YES ☐ ! NO ☐
 ! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form:
Celia R. Peacock, MPH, RD
Title: Regulatory Project Manager
Date: October 14, 2008

Name of Office/Division Director signing form:
George Benson, MD
Title: Deputy Division Director, Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-030 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DRUP PDUFA Goal Date: 11/02/08 Stamp Date: 5/2/2008

Proprietary Name: Toviaz

Established/Generic Name: fesoterodine fumarate

Dosage Form: Tablets, 4 mg, 8 mg

Applicant/Sponsor: Pfizer, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

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

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

(a) NEW ☒ active ingredient(s); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

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

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

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

Indication: Overactive Bladder (OAB)

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

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

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for the remaining pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

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

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

☐ Justification attached.

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

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

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 0 mo.	4 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

\# Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

Δ Formulation failed:

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

☐ Justification attached.

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

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☒	Other	5 yr. 0 mo.	17 yr. 11 mo.	☒	☐	☐	☒	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

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

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

* Other Reason:

Please note*** This is a resubmission to NDA 22-030, a Complete Response to a 1/25/07 Approvable Letter and has a 6 month PDUFA clock.

To maintain consistency with other similar OAB products, we are recommending that the sponsor waive clinical studies in the age group 0 - 4, and defer for ages 5 - 17.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be

conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 4/2008)

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

Attachment A

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

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

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

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

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

☐ Justification attached.

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

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

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

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

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

\# Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

☐ Justification attached.

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

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

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

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

* Other Reason: _____

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

If there are additional indications, please 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: 4/2008)

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

/s/

Celia R Hayes
8/4/2008 12:34:39 PM

DEBARMENT CERTIFICATION

SCHWARZ BIOSCIENCES, INC. herby 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.

27 Jan 2006 Richard Todd

Date/Signature

Richard Todd
Associate Director
Clinical Quality Assurance

Peacock, Celia

From: Greeley, George
Sent: Friday, October 10, 2008 11:21 AM
To: Peacock, Celia
Subject: RE: Meeting Minutes from Toviaz (fesoterodine fumarate)?

Toviaz Partial Waiver/Deferral/Pediatric Plan

- NDA 22-030, Toviaz (fesoterodine fumarate) Tablets, was studied for overactive bladder. This application was submitted on May 2, 2008, and has a PDUFA date of November 2, 2008.
- The PeRC had questions about the indication and the Division responded that the neurogenic bladder problems experienced by patients with spina bifida are a subset of overactive bladder.
- The PeRC asked why patients under 5 years should not be included in the studies. The Division stated that they wanted to be consistent with how they had handled similar applications in the past. There is nothing novel about this drug other than the sponsor. The Division plans to grant a partial waiver because it is too difficult to study patients under 5.
- The PeRC recommended changing the Pediatric Page to reflect the partial waiver that is being granted, not the partial waiver the sponsor requested, which was for patients under 6 years.
- The PeRC agreed with the partial waiver for patients less than 5 years.
- The PeRC recommended changing the reason for deferral on the Pediatric Page to reflect that the product is ready for approval in adults.
- The PeRC recommended that the Division add the dates for the protocol submission and the date the studies are due to the AP letter. Also, they should be sure the AP letter reflects both studies to be conducted.
- The PeRC agreed with the deferral and plan.

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Draft
10/23/08

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-030 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Toviaz Established/Proper Name: Fesoterodine fumarate Dosage Form: Tablets		Applicant: Agent for Applicant (if applicable):
RPM: Celia Peacock		Division: HD-580

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **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.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	10/31/2008
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	Approvable Action Taken 1/25/2007
❖ Promotional Materials *(accelerated approvals only)*. 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 www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] 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[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	7/09/2008
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

.ll 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
Copy of this Action Package Checklist[3]	10/31/2008
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Actions and dates: 10/31/08 Approval 1/25/07 Approvable
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	10/08/08
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	5/02/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	VESIcare, Enablex and Detrol LA.
Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☒ Patient Package Insert

[3] Fill in blanks with dates of reviews, letters, etc.

	☐ Instructions for Use ☐ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	10/14 /08
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	5/02/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission) • Most recent submitted by applicant	10/ /08 10/14/08
• Most recent applicant-proposed labeling	5/02/08
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP 10/16/08; 1/11/07, 7/18/06 ☒ DRISK 9/10/08; 10/14/08; 7/31/06 ☒ DDMAC 7/25/08; 11/16/05 ☐ CSS ☒ Other reviews Maternal Health 9/18/08
Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	10/16/08; 1/11/07; 11/18/05; 11/16/05
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	6/13/06 RPM
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submissions/communications	
Postmarketing Commitment (PMC) Studies	Deferred Pediatric Study PREA Requirement
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	Meeting Date: 7/09/08
• Pre-Approval Safety Conference *(indicate date; approvals only)*	Meeting Date: 10/22/08
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	Meetings Date: 7/18/05 and 11/22/05 (CMC)
• EOP2 meeting *(indicate date)*	Meeting Date: 6/16/03
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
Office Director Decisional Memo *(indicate date for each review)*	10/ /08, 1/25/07, 1/22/07
Division Director Summary Review *(indicate date for each review)*	10/23/08
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/21/08
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	10/21/08, 10/25/07
• Clinical review(s) *(indicate date for each review)*	10/7/08, 7/3/08, 1/17/07
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See Medical Officer Review 10/07/08
❖ 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	10/20/08 Memo
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

• REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	1/18/07
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	10/20/08
Statistical Review(s) *(indicate date for each review)*	1/10/07, 7/26/06
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	
Clinical Pharmacology review(s) *(indicate date for each review)*	7/3/08, 9/02/08, 12/05/06
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	9/11/08, 1/22/07
• Supervisory Review(s) *(indicate date for each review)*	9/25/08, 12/25/08, 12/20/06
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	6/09/08, 9/16/08, 12/12/06, 5/11/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	7/18/06
❖ ECAC/CAC report/memo of meeting	7/14/06, 8/28/02
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	10/16/08
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	5/24/06
• CMC/product quality review(s) *(indicate date for each review)*	9/11/08, 1/19/07, 5/24/06
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed

❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review Page 24 - dated 9/11/08
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: See pages 25 – 29 CMC Review dated 9/11/08 Shannon IR site reviewed and found acceptable on July 15, 2008 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ 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 DRA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-030

INFORMATION REQUEST LETTER

Schwarz Biosciences
Attention: Alan Blumberg, Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Dr. Blumberg:

Please refer to your March 17, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fesoterodine fumerate, 4 and 8 mg tablets.

The Division of Medication Errors and Technical Support (DMETS) and Division of Drug Marketing, Advertising, and Communications (DDMAC) have completed their review of the proposed proprietary name, and the container/carton labeling. In conjunction with these Divisions, we have the following recommendations and comments.

In regard to the proprietary name:

1. DMETS has no objections to the use of the proprietary name, [redacted] This is considered a tentative decision. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval is necessary to rule out any objections based upon approval of other proprietary or established names from the signature date of this document. b(4)

2. DDMAC finds the proprietary name [redacted] acceptable from a promotional perspective.

In regard to the carton labeling:

1. [redacted] b(4)

2. [redacted] b(4)

b(4)

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at 301-796-0952.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Mark S. Hirsch
1/31/2007 02:46:14 PM

Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE OF DRUG EVALUATION
ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2007

To: Alan Blumberg, Ph.D.
Senior Director, Regulatory Affairs
Company: Schwarz Pharma

Fax number: 919-767-3139

Phone number: 919-767-2513

From: Jean Makie

Division of Reproductive and Urologic Products
Fax number: 301-796-9798

Phone number: 301-796-0952

Subject: NDA 22-030: Approvable letter

Document to be mailed: YES NO

Dear Alan,

As discussed during today's telephone conversation with you, please find attached a copy of the Agency's Approvable action letter for NDA 22-030, fesoterodine fumarate for the treatment of overactive bladder (OAB). You will also receive this letter via postal mail.

Best regards,

Jean Makie
Sr. Regulatory Project Manager

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

/s/

Jean Makie
1/25/2007 12:48:10 PM
CSO

Jean Makie
1/25/2007 12:54:54 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 22-030	Efficacy Supplement Type SE- N/A	Supplement Number: N/A	
Dru ~~(fesoterodine fumarate)~~		Applicant: Schwarz Pharma b(4)	
RPM: Jean Makie, M.S., R.D.		HFD-580	Phone # 301-796-0952
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	January 27, 2007; action goal date: 1/26/07
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	N/A for approvable action
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (**X**) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	() AP ( ) TA (**X**) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	() Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (**X**) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(**X**) None ( ) Press Release () Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X [7/17/03 and 7/13/2004 (CMC)]
• Pre-NDA meeting (indicate date)	X [7/18/05 and 1/22/05 (CMC)]
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (see clinical review)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (EA acceptable; See Chemistry Review)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	() Acceptable **(X)** Withhold recommendation Sponsor's drug substance manufacturing site (Shannon, Ireland) is not ready for Pre-Approval Inspection (PAI).
❖ Methods validation	( ) Completed ( ) Requested **(X)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X
❖ CAC/ECAC report	X

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

/s/

Jean Makie
1/24/2007 03:31:59 PM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE:	January 18, 2007
TO:	Jean Makie, Regulatory Project Manager Suresh Kaul, M.D., Medical Officer Division of Reproductive and Urologic Drug Products
THROUGH:	Constance Lewin, M.D., M.P.H. Chief, Good Clinical Practice Branch I (GCPB1, HFD-46) Division of Scientific Investigations (DSI)
FROM:	Roy Blay, Ph.D. Reviewer, GCPB1, DSI, HFD-46
SUBJECT:	Evaluation of Clinical Inspections
NDA:	22-030
APPLICANT:	Schwarz Biosciences
DRUG:	Fesoterodine hydrogen fumarate
THERAPEUTIC CLASSIFICATION:	Standard
INDICATION:	Treatment of overactive bladder
CONSULTATION REQUEST DATE:	June 5, 2006
DIVISION ACTION GOAL DATE:	November 20, 2006
PDUFA DATE:	January 27, 2007

I. BACKGROUND

The indication for the investigational drug fesoterodine hydrogen fumarate is for the treatment of overactive bladder. It is not a new molecular entity. In support of this NDA, FDA inspected protocols SP583 and SP584, both entitled "A Phase 3, Parallel Group, Randomized, Double-Blind, Double Dummy, Placebo and Active Controlled Multicenter Trial to Investigate the Efficacy, Tolerability, and Safety of Fesoterodine Sustained Release in Subjects with Overactive Bladder Syndrome".

The primary efficacy endpoint for both protocols is the change in average number of micturitions (frequency) per 24 hours (from baseline to value after 12 weeks of treatment). The co-primary variable for protocol SP584 is the change in average number of urge incontinence episodes per 24 hours (from baseline to value after 12 weeks of treatment). The co-primary variable for protocol SP583 is the treatment response (as yes/no variable), derived from a treatment benefit scale.

The following domestic and foreign sites were selected for inspection because they were among the largest enrollers. The domestic sites conducted protocol SP584 and the foreign sites, SP583.

II. RESULTS (by site):

Name and Site #	City, State, Country	Protocol	Inspection Date	EIR Received Date	Final Classification
onald Bergner, M.D. (#006)	Clearwater, FL	SP 584	23 Oct-7 Nov 06	27 Nov 06	VAI*
Steven Elliot, M.D. (#027)	Evansville, IN	SP 584	5-12 Sep 06	9 Oct 06	VAI
Heino-Enn Arpo, M.D. (#036)	Tallinn, Estonia	SP 583	20-24 Nov 06	pending	VAI*
Gennadi Timberg, M.D. (#039)	Tartu, Estonia	SP 583	27 Nov-Dec 06	pending	NAI*

*preliminary, pending receipt and review of the EIRs

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # SP 584

1. Site # 006
   Donald Bergner, M.D.
   Tampa Bay Medical Research, Inc.
   3251 McMullen Booth Rd., Suites 301/303
   Clearwater, FL 33761
   and
   3890 Tampa Road, Suite 102
   Palm Harbor, FL 34684
   and
   Urology Consultants
   33920 US Highway 19 N, Suite 241
   Palm Harbor, FL 34684

   a. What was inspected: Forty-six subjects were enrolled with 29 subjects discontinued by Visit 2 and 17 subjects completing the study, The records of approximately 20 subjects were audited in depth. The audit included, but was not limited to, review of source documentation, sonography results, laboratory data, informed consent, ECGs, the primary efficacy endpoint, and adherence to inclusion/exclusion criteria.

   b. Limitations of inspection: There were no limitations to the inspection.

   c. General observations/commentary: The inspection revealed that seven of seventeen diaries reviewed were not completed properly. The diaries for subjects 13087, 13101, 13321, 13484, 13700, 13856, and 14682 contained numerous errors including, but not limited to, blanks, deletions or revisions without explanations, repetition of data for multiple days, and data that were physiologically improbable (e.g., multiple micturitions on Day 1 with no record of any micturitions on Days 2 and 3). These errors were reflected in the line listing calculations of mean number of voids per day. In addition, review of sixteen subject records revealed at least four subjects did not have their residual urine volumes determined appropriately.

Subject #	residual urine volume (mL)
13009	>86
13072	>96
13087	>36
14687	>62

   It could not be determined whether these subjects met the exclusion criterion of having a residual urine volume of greater than 100 mL at Visit 2.

d. Data acceptability/reliability: The data from the seven subjects noted above, whose diaries contain substantial errors, appear unacceptable. In addition, four of sixteen subjects may have been inappropriately enrolled (i.e., may have met an exclusion criterion) because of incorrect testing procedures (i.e., residual urine volume determinations). The review division should carefully consider the deficiencies in these data and whether these data from this site should be excluded from their safety and/or efficacy analyses for this application.

2. Site #027
Steven Elliot, M.D.
MediSphere Medical Research Center, LLC
1401 Professional Blvd., Suite 100
Evansville, IN 47714
and
MediSphere Medical
Research Center, LLC
2345 W. Franklin Street, Suite 202
Evansville, IN 47712
and
Urological Associates, Inc.
920 S. Hebron Av.
Evansville, IN 47714

a. What was inspected: The records for all 12 subjects enrolled in the study were audited in depth. Records reviewed included, but were not limited to, CRFs, EKGs, residual urine sonograms, adverse event reporting, drug accountability records, hematology and chemistry lab results, and physical examinations

b. Limitations of inspection: There were no limitations to this inspection.

c. General observations/commentary: The inspection revealed deviations from the investigational plan in that subjects 13222 and 14847 were inappropriately randomized to the study despite having met exclusion criteria of excessive polyuria.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

B. Protocol SP 583

1. Site #039
Gennadi Timberg, MD
Tartu University Clinics
Departement of Urology and Kidney Transplantation
8 Puusepa Street
Tartu 51014
Estonia

a. What was inspected: The records for 20 subjects were audited in depth.

b. Limitations of inspection: Any significant limitations of the inspection will be communicated, if necessary, after receipt and review of the EIR.

c. General observations/commentary: Inspection did not reveal any regulatory violations.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication. These observations and conclusions are based solely upon the review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Site #036
Heino-Enn Arpo, M.D.
Pelgulinna Hospital
Department of Urology
Sõle Street 16
Tallinn 10611
Estonia

a. What was inspected: The number of records reviewed and the scope of that review will be described after receipt and review of the EIR.

b. Limitations of inspection: Any significant limitations of the inspection will be communicated, if necessary, after receipt and review of the EIR.

c. General observations/commentary: The Form FDA 483 issued at the conclusion of the inspection consisted of a single observation related to inadequate/inaccurate records in that an adverse event of severe diarrhea for subject 11336 was reported in the source data but not recorded in the adverse event section of the CRF. Dr. Arpo's written response acknowledged that this adverse event was not recorded on the CRF.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication. The above observation and conclusion are based solely upon the review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Elliot, Arpo, and Timberg did not identify any significant regulatory violations. Overall, the data appear acceptable in support of the respective indication. This assessment and recommendation for Drs. Arpo and Timberg are based solely upon the review of the Form FDA 483s. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

The inspection of Dr. Bergner revealed deficiencies with diary entries for seven of 17 subjects and the determination of residual urine volumes for four of sixteen subjects. Given the extent of these deficiencies, the review division may wish to consider whether to exclude these data from its safety and/or efficacy analyses.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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

/s/

Roy Blay
1/18/2007 01:55:32 PM
CSO

Constance Lewin
1/18/2007 02:09:29 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-030

INFORMATION REQUEST LETTER

Schwarz Biosciences
Attention: Alan Blumberg, Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Dr. Blumberg:

Please refer to your March 17, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fesoterodine fumerate, 4 and 8 mg tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Because the engravure for the tablets used in the clinical trial was [redacted] the acceptance criteria for "Appearance" in the specifications and the tablet description in the "How Supplied" section of the labels should state that the engravure is [redacted] If there are any changes to the engravure, you should perform comparative dissolution testing to demonstrate that the tablets are comparable, and the acceptance criteria for "Appearance" in the specifications and the tablet description in the "How Supplied" section of the labels must reflect any change. b(4)

2. Based on review of your submitted data, tighten the release and stability acceptance criteria of impurities/degradation products in the drug product as follows:

Degradation products (at release)	Your proposal (4 mg)	Your proposal (8 mg)	FDA (4 and 8 mg)
[redacted]			
Any other single impurities			
Total degradation products			

b(4)

Degradation products (at Stability)	Your proposal (4 mg)	Your proposal (8 mg)	FDA (4 and 8 mg)
Any other single impurities			
Total degradation products			

b(4)

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at 301-796-0952.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Moo-Jhong Rhee
12/13/2006 10:36:29 AM
Chief, Branch III

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: NDA 22-030, Requested Tradename: None at present; [redacted] previously submitted to IND 51,232. DMETS and DRUP found [redacted] acceptable, however, [redacted] was found fanciful and unacceptable. b(4)

Generic: fesoterodine fumarate, 4 and 8 mg extended release tablets

Date of Application:	March 17, 2006
Date of Receipt:	March 27, 2006
PDUFA Date:	January 27, 2007
Action Goal Date:	January 26, 2007

Indication(s) requested: for the treatment of overactive bladder

Type of Application: Full NDA ___X___ Supplement _____
(b)(1) ___X___ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S__X__ P_____
Resubmission after a withdrawal or refuse to file __N/A__
Chemical Classification: (1,2,3 etc.) 1S
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug 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 the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ___X___ Waived (e.g., small business, public health) _____
Exempt (orphan, government) ____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID# 3006442
Clinical data? YES ___X___ NO _____ Referenced to NDA#

Date clock started after UN _____N/A_____

User Fee Goal date: January 27, 2007

Action Goal Date (optional) January 26, 2007

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:
- If electronic NDA, does it follow the Guidance? YES NO

  If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO
- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES; If yes, ___ years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."
- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:

  * The sponsor requested in this NDA submission a partial waiver for ages 0-5 years. The Sponsor also requested a deferral for proposed pediatric clinical studies in children ages 6-16 years old.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO

If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 51,232

End-of-Phase 2 Meeting? Date 7/17/03 and 7/13/2004 (CMC)

If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date 7/18/05 and 1/22/05 (CMC)
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI and PPI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?

YES NO

Requested Tradename: None at present; [redacted] were previously submitted to IND 51,232. b(4)
DMETS and Division found [redacted] acceptable, however, [redacted] was found fanciful and unacceptable.
An Advice letter was sent to Sponsor at that time. A second consult will be sent to DMETS when the Sponsor submits a proposed trade name.

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO N/A

*N/A: This is not an application for an OTC product.

Advisory Committee Meeting needed? YES, date if known NO

Clinical

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

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
- If no, did sponsor submit a complete environmental assessment? YES NO

If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following: Not applicable

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO
If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

NDA 22-030: Filing Meeting Minutes

NDA: 22-030 **Sponsor:** Schwarz Pharma **Drug:** Fesoterodine fumarate

Date: May 11, 2006 **Time**: 10:00 – 11:30 AM

FDA/CDER/DRUDP Attendees:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)
Suresh Kaul, M.D., Medical Reviewer, DRUP
Roger Wiederhorn, M.D., Medical Reviewer, DRUP
Doanh Tran, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP) @ DRUP
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, OCP @ DRUP
Jean Makie, M.S., R.D., Sr. Project Manager, DRUP
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff, DRUP
Laurie McLeod-Flynn, Ph.D., Pharmacology/Toxicology Reviewer, DRUP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUP
Rajiv Agarwal, Ph.D., Chemistry Reviewer, Initial Quality Assessment Branch III, Pre-Marketing Assessment Division II @ DRUP
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Initial Quality Assessment Branch III, Pre-Marketing Assessment Division II @ DRUP
Mahboob Sobhan, Biometrics Team Leader, Division of Biometrics 2, Office of Biostatistics @ DRUP

Issues Discussed:

On March 27, 2006, a new drug application (NDA 22-030) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fesoterodine fumarate for the treatment of overactive bladder (OAB). During this filing review meeting, the following issues were discussed:

Clinical

- The application is fileable.

The following review issues were identified. Clinical comments #4-8 will be conveyed to the Sponsor in the 74-Day letter.

1. Preliminary review of the safety data from the pivotal studies (SP583, SP584) reveals only those adverse events that are commonly associated with the anticholinergic drug class (e.g. dry mouth, constipation, and urinary retention). No new types of events and no serious drug-related adverse events were reported.

2. Preliminary review of data from the thorough QT study (SP686) does not appear to suggest that fesoterodine is associated with QT prolongation or other abnormal cardiac conduction.

3. There are no clearly apparent deficiencies in the labeling based upon the initial filing review.

4. There are several individual adverse event reports that will require additional Clinical review, including:
    i. Pancreatitis in one patient
    ii. Electrocardiographic evidence of QT prolongation in two patients
    iii. 2-fold increases in serum ALT in several patients
    iv. Sponsor should submit an executive summary of these cases with emphasis on possible drug causality.

5. The study population is predominantly White (92%). There is no reason to suspect a difference in safety or efficacy between White and non-White patients, but this will be a review issue.

6. Fesoterodine was associated with a mean increase in the heart rate of 2- 6 beats per minute in the general OAB population in the Phase 3 studies. Sponsor should provide an analysis of the potential risks associated with this pharmacodynamic effect, and should propose risk management measures that may minimize the overall risks of an increase in heart rate (e.g. specific labeling).

7. Increase in residual urine volume was observed in both Phase 3 studies, with a greater increase seen in males compared to females. Excessive increase in residual urine volume, especially in males, will be a safety review issue.

8. The predominant metabolic pathway for SPM 7605 is via CYP2D6 metabolism. Clinical adverse events in poor metabolizers will be compared to those in extensive metabolizers. This will be a review issue.

9. Clinical investigational sites have been selected for inspection. These will be conveyed to DSI in a formal consult request.

Clinical Pharmacology

- The application is fileable.

The following review issues were identified. Clinical Pharmacology comments #1-4 will be conveyed to the Sponsor in the 74-Day letter.

1. We only found pharmacokinetic (pk) data files for study SP686. Help us locate pk data files for all other studies or submit them to us in SAS transport format, along with associated data definition files.

2. The effect of alcohol consumption on the integrity of the modified release formulation was not examined. Provide data on alcohol effect or rationale in support of the lack of need for such study in this NDA.

3. The AUC and Cmax changes in CYP2D6 poor metabolizers, renal and hepatic impaired patients, and concomitant administration of CYP2D6 inhibitors or CYP3A4 inhibitors and inducers will be reviewed with respect to safety and efficacy. Modification of the labeling may be necessary.

4. The Sponsor included bridging bioequivalent data for 2 x 4 mg tablets of formulation B (used in phase 1 and 2 trials) to 1 x 8 mg tablet of formulation D (used in phase 3 trials). There was no bioequivalent data comparing 1 x 4 mg formulation B to 1 x 4 mg formulation D. This will be a review issue.

5. Discussion ensued in regard to the need to link the to-be-marketed formulation F ——— to the clinical trial material: formulation F ———. Clinical Pharmacology agreed with Chemistry that additional comparisons of in vitro dissolution profiles in three media will be necessary to link the two formulations. b(4)

Statistics

- The application is fileable.
- No review issues noted at time of filing.

Pharmacology/Toxicology

- The application is fileable.
- No review issues were noted at time of filing.
- A statistical consult was obtained for the carcinogenicity studies. Although there is a delay in elimination from ocular tissues, preliminary review of histopathology data reveals no toxicity.

Chemistry

- The application is fileable.

The following review issues will be conveyed to the Sponsor in the 74-Day Letter:

- The Sponsor should submit multi-point dissolution profiles in additional buffers as per the SUPAC-MR guidance for a Level 2 manufacturing change to compare drug product manufactured using the ——— (Formulation F) and ——— (Formulation F, to-be-marketed tablets) processes. b(4)

- The Sponsor should submit confirmation that the Schwarz Parma site in Shannon, Ireland is the same as the SIFA Ltd site (CFN 9610732) that is listed in the FDA database under the same address.

- The Sponsor should submit information to clarify a) what controls are in place to assure that the drug substance is stored at the correct temperature range during shipping, and b) whether the drug substance is tested at the drug product manufacturing facility prior to use to assure that the degradation due to moisture and temperature sensitivity has not occurred.

- The Sponsor should confirm that the engravure for the tablets is ' ——as stated in the General Correspondence dated 12-Jan-2006. If this is not correct, the Sponsor should provide the correct information. b(4)

- An additional time point should be added to the dissolution specifications between the 4 hour and 16 hour draws. We recommend a draw at either 8 or 10 hours. Submit a proposal.

- If a decision is made to package drug product in blisters for commercial distribution, the blister packs should be child resistant.

- The Sponsor should submit additional stability data as soon as it becomes available in order to determine expiry.

- The drug product is an extended-release tablet, and although the Sponsor refers to it as sustained release throughout the NDA submission, they are aware that the correct terminology for the US market is extended-release and the proposed packaging is labeled to reflect this.

- The Sponsor has not proposed a trade name with the submitted labeling. The Sponsor should submit a proposed trade name as soon as it becomes available. At that time, a trade name consult and container/carton labeling will be sent to ODS/DMETS for their review.

In terms of other consults:

- The PI and PPI will be sent to DDMAC.

- The PI will be sent to DMETS.

- The PPI will be sent to DSRCS.

Summary of Action Items:

- NDA 22-030 is fileable. We will provide comments regarding all unresolved issues noted above to the sponsor as preliminary notice of potential review issues in a 74-day Filing Letter. 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. The Sponsor will also be informed that if they respond to these issues during this review cycle, we may not consider their response before we take an action on their application.

- We will follow the GRMP guidance.

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

/s/

Jean Makie
6/13/2006 11:39:17 AM
CSO

Filing minutes are attached at end of this review

Mark S. Hirsch
6/16/2006 06:00:05 PM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: June 13, 2006

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

Through: Joseph Salewski, Acting Director
Division of Scientific Investigations, HFD-45
Daniel Shames, Md., F.A.C.S., Director, Division of Reproductive and Urologic Products, HFD-580

From: Jean Makie, Sr. Regulatory Health Project Manager
Division of Reproductive and Urologic Products, HFD-580

Subject: **Amended Request for Clinical Site Inspections**
Application: NDA 22-030
Sponsor: Schwarz Pharma
Drug: fesoterodine fumerate

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: *New indication*

This drug is a New Molecular Entity (NME).

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
		14	Overactive bladder

b(4)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
[redacted]		11	Overactive bladder
Site # 006: Dr. Donald Bergner, M.D. Tampa Bay Medical Research, Inc. 3251 McMullen Booth Rd. Suites 301/303 Clearwater, FL 33761 and 3890 Tampa Road, Suite 102 Palm Harbor, FL 34684 and Urology Consultants 33920 US Highway 19 N, Suite 241 Palm Harbor, FL 34684 **Phone: 727-724-3316** **Fax: 727-725-5561**	SP 584	42	Overactive bladder

b(4)

b(4)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Site #027: Dr. Steven Elliot, M.D. MediSphere Medical Research Center, LLC 1401 Professional Blvd., Suite 100 Evansville, IN 47714 and MediSphere Medical Research Center, LLC 2345 W. Franklin Street, Suite 202 Evansville, IN 47712 and Urological Associates, Inc. 920 S. Hebron Av. Evansville, IN 47714 **Phone: 812-471-4110** **Fax: 812-471-4275**	SP 584	56	Overactive bladder

Domestic Inspections:

We have requested inspections because (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): Pivotal study

International Inspections:

We have requested inspections because (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): Pivotal study with enrollment of large numbers of study subjects

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by **November 1, 2006**. We intend to issue an action letter on this application by **January 26, 2007**. The PDUFA due date for this application is ***January 27, 2007.***

Should you require any additional information, please contact Jean Makie, Sr. Regulatory Project Manager at Ph: 301-796-0952

Sponsor Contact: Alan Blumberg, Ph.D.
Senior Director, Regulatory Affairs
Fax number: 919-767-3139

Phone number: 919-767-2513

Concurrence:
Mark Hirsch, M.D., Medical Team Leader
Suresh Kaul, M.D., Medical Reviewer
Daniel Shames, M.D., F.A.C.S, Division Director (for foreign inspection requests only)

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

/s/

Jean Makie
6/13/2006 09:37:19 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-030

Schwarz Biosciences
Attention: Alan Blumberg, Ph.D.
Senior Director, Global Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Dr. Blumberg:

Please refer to your March 17, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fesoterodine fumarate, 4 and 8 mg extended release tablets.

We also refer to your submissions dated May 15, 17 and 23, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 26, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical

1. There are several individual adverse event reports that will require additional Clinical review, including:
    i. Pancreatitis in one patient
    ii. Electrocardiographic evidence of QT prolongation in two patients
    iii. 2-fold increases in serum ALT in several patients

    Submit an executive summary of these cases with emphasis on possible drug causality.

2. The study population is predominantly White (92%). While there is no apparent reason to suspect a difference in safety or efficacy between White and non-White patients, this will be a review issue.

3. Fesoterodine was associated with a mean increase in the heart rate of 2- 6 beats per minute in the general overactive bladder (OAB) population in the Phase 3 studies. Provide an analysis of the potential risks associated with this pharmacodynamic effect,

and propose risk management measures that may minimize the overall risks of an increase in heart rate (e.g. specific labeling).

4. Increase in residual urine volume was observed in both Phase 3 studies, with a greater increase seen in males compared to females. Excessive increase in residual urine volume, especially in males, will be a safety review issue.

5. The predominant metabolic pathway for SPM 7605 is via CYP2D6 metabolism. Clinical adverse events in poor metabolizers will be compared to those in extensive metabolizers. This will be a review issue.

Clinical Pharmacology

1. We only found pharmacokinetic (pk) data files for study SP686. Submit the pk data files in SAS transport format, along with the associated data definition files, for all other studies to the NDA.

2. The effect of alcohol consumption on the integrity of the extended release formulation was not examined. Provide data on alcohol effect or rationale in support of the lack of need for such study in this NDA.

3. The AUC and Cmax changes in CYP2D6 poor metabolizers, renal and hepatic impaired patients, and concomitant administration of CYP2D6 inhibitors or CYP3A4 inhibitors and inducers will be reviewed with respect to safety and efficacy. Modification of the labeling may be necessary.

4. You have included bridging bioequivalent data for 2 x 4 mg tablets of formulation B (used in phase 1 and 2 trials) to 1 x 8 mg tablet of formulation D (used in phase 3 trials). There was no bioequivalent data comparing 1 x 4 mg formulation B to 1 x 4 mg formulation D. This will be a review issue.

Chemistry

1. Submit information to clarify a) what controls are in place to assure that the drug substance is stored at the correct temperature range during shipping, and b) whether the drug substance is tested at the drug product manufacturing facility prior to use to assure that degradation due to moisture and temperature has not occurred.

2. Confirm that the engravure for your tablets is —— , as stated in the General Correspondence dated 12-Jan-2006. If this is not correct, provide the correct information. Also clarify whether the clinical trial supplies had the same engravure. b(4)

3. An additional time point should be added to the dissolution acceptance criteria between the 4 hour and 16 hour draws. We recommend a draw at either 8 or 10 hours. Please submit a proposal.

4. Be aware that, if a decision is made to package drug product in blisters for commercial distribution, the blister packs would need to be child resistant.

5. Submit additional stability data as soon as it becomes available in order to determine expiry date.

6. Submit proposed tradename(s) to allow complete review of the labeling.

7. We remind you of your commitments:

b(4)

   i. To complete comparative dissolution profiles for formulation F, [redacted] in water, 0.1 N HCL, and pH 4.5 buffer and to submit this data as soon as possible.
   ii. To be ready for pre-approval inspection of the API manufacturing facility located in Shannon, Ireland on (but no later than) September 27, 2006.

We are providing the above 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.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at (301) 796-0952.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Daniel A. Shames
6/9/2006 10:20:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-030

NDA ACKNOWLEDGMENT

Schwarz Biosciences
Attention: Alan Blumberg, Ph.D.
Senior Director, Global Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Dr. Blumberg:

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:	Fesoterodine fumarate
Review Priority Classification:	Standard (S)
Date of Application:	March 17, 2006
Date of Receipt:	March 27, 2006
Our Reference Number:	NDA 22-030

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 May 26, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 26, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies to be conducted in 0-5 year old children and a deferral of pediatric studies to be conducted in 6-16 year old children for this application. Once the application has been filed, we will notify you whether we have waived and/or deferred the pediatric study requirements for this application.

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

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

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at (301) 796-0952.

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

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

/s/

Margaret Kober
4/17/2006 03:30:37 PM
Chief, Project Management Staff

IND 51,232: FDA Preliminary Draft Comments for November 22, 2005 Pre-NDA CMC meeting

Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2005

To: Alan Blumberg, Ph.D., Sr. Director, Regulatory Affairs

Company: Schwarz Pharma

Fax number: 919 -767- 3139

Phone number: 919-767-2513

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-796-9897

Phone number: 301-796-0952

Subject: IND 51,232: Preliminary draft comments for the 11/22/05 Pre-NDA CMC meeting

NOTE: This document contains preliminary notes to help you prepare for the meeting scheduled for November 22, 2005. This material is shared with you solely to promote a collaborative and successful discussion at the meeting. This should not be considered as the official position of the FDA. Official minutes will be recorded at the meeting to reflect agreements and discussions and may not be consistent with these reviewers' preliminary notes. Please bear in mind that additional questions that have not been reviewed by the Division will not be entertained.

Document to be mailed: **YES** **NO**

DRAFT RESPONSES/COMMENTS

Pre-NDA, Type B Guidance Meeting: Fesoterodine (SPM 8272)

Schwarz Pharma, IND#51,232

Sponsor's Questions:

Q 1:

b(4)

Division Response:

b(4)

Q 2: Does the Agency agree that the proposed shelf life of months is acceptable, based on the extensive amount of stability data available.

Division Response:

b(4)

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

/s/

Jean Makie
11/28/2005 02:04:19 PM
CSO

Jean Makie
11/28/2005 02:06:40 PM
CSO

MEETING MINUTES

Date: June 16, 2003 **Time:** 11:00 AM - 12:30 PM **Location:** PKLN Potomac

IND: 51,232

Drug Name: Fesoterodine

Sponsor: Schwarz BioSciences

Type of Meeting: End of Phase 2

Meeting Chair: Mark Hirsch

Meeting Recorder: Margaret Kober

External Lead: Alan Blumberg

FDA Attendees:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Daniel Davis, M.D., Medical Officer, DRUDP
Laurie McLeod, Ph.D., Pharmacologist, DRUDP (HFD-580)
Mike Welch, Ph.D., Biostatistics Team Leader, DRUDP
DJ Chatterjee, Ph.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB @ DRUDP, HFD-580)
Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, OCPB @ DRUDP, HFD-580
Margaret Kober, RPh., Chief, Project Management Staff, DRUDP

External Attendees:

Alan Blumberg, Ph.D., Senior Director, Regulatory Affairs, US
Iris Deis, Ph.D., Associate Director, Regulatory Affairs, Germany
Hans-Theo Forst, Ph.D., Director, Biostatistics, Germany
Cornelia Haag-Molkenteller, M.D., Vice President, Therapeutic Area Urology, Germany
Ute Massow, Ph. D., Clinical Program Director, Therapeutic Area Urology, Germany
Richard Sachse, M.D., Senior Scientist, Clinical Pharmacology, Germany
Ute Scharfencker, Ph.D., Senior Scientist, Pharmacokinetcs/ADME, Germany
Andrea Schuetz, International Project Manager, Germany
Chip Sherrill, Medical Writer, US

Background: Fesoterodine hydrogen fumarate (SPM 8272) is a product under development as a sustained release, once daily formulation for the proposed indication of overactive bladder syndrome defined as urgency, [redacted] urge incontinence, [redacted] A European trial was completed in December, 2002. The background package for an end of Phase 2 meeting was received May 2, 2003 as Submission N-048. b(4)

Meeting Objectives: The purpose of the meeting was to obtain the agency's advice concerning the proposed Phase 3 program.

Discussion Points:

Questions and Answers:

1. Does the agency agree that no dose reduction is needed in the Phase 3 program in any sub-population (considering the inclusion and exclusion criteria of the Phase 3 protocols)?

- Yes, but dose reduction may be required in labeling. For example, the dose used in the ketoconazole drug interaction study may not be high enough to address concerns in the sub-population of patients taking concomitant ketoconazole. We recommend a study which includes a 200mg dose of ketoconazole twice daily. Justification for the dose selected in the completed study may suffice in lieu of an additional study. (This will be a review issue.)

- Additionally, renal, hepatic, and interaction studies using several other drugs are needed to address labeling for dose reduction in other sub-populations.

- Poor metabolizers should be included in Phase 3 trials to determine the need for dose reduction in this sub-population.

- Sponsor has agreed to conduct genotyping in the US Phase 3 trial.

- Sponsor needs to demonstrate the 4mg is generally the lowest effective dose. The division recommends that a lower dose be explored, as it may be needed by some individuals and by specific sub-populations. Justification (using dose-response analysis) may suffice in lieu of clinical studies of a lower dose. (This will be a review issue.) b(4)

2. Based upon the pharmacokinetic and safety data in the ketoconazole interaction trial (SP564), Schwarz believes [redacted] for fesoterodine when co-administered with CYP 3A4 inhibitors. Does the Agency agree with this view?

- It is premature to answer at this time. The clinical relevance of increased exposures is not yet known and should be addressed in Phase 3. We would expect a dose reduction similar to that described in the tolterodine labeling. This will be a review issue.

3. Does the Agency agree that there is no need to perform additional trials investigating the interaction potential on the cytochrome [redacted] level? b(4)

- No. We recommend conducting studies with a 3A4 inducer and a 2D6 inhibitor.

4. Does the Agency agree that the Phase 3 protocols outlined in the submission will support the indication overactive bladder syndrome defined as "*urgency,* [redacted] *urge incontinence,* [redacted] (ICS definition, 2002) b(4)

- No. The current indication for overactive bladder syndrome ("_____ is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.") would only be supported by trials which demonstrate substantial evidence of efficacy for both micturition frequency and urge incontinence. If both endpoints are not met, the application may still be approved, but the exact wording of the indication will be a review issue.

5. Does the Agency agree that the doses of 4 and 8mg are the appropriate doses to be further investigated in Phase 3 studies?

- We have no objection to studying 4mg and 8mg in the Phase 3 trials. However, the sponsor should also ultimately provide evidence that a lower dose, such as 2mg, is not effective.

6. Does the Agency agree to the hierarchy of primary variables proposed for the Phase 3 protocols?

b(4)

- No. When reviewing drug applications for overactive bladder syndrome, we consider micturition frequency, urge incontinence episode frequency, and volume voided to be the three critical efficacy endpoints. Approval is possible if efficacy is demonstrated for micturition frequency in 2 trials. Most compelling would be substantial evidence of efficacy for both micturition frequency and urge incontinence episode frequency. We recommend that micturition frequency be a primary endpoint and that urge incontinence episode frequency be either a co-primary or critical secondary endpoint. We recommend one of two options for the hierarchy:

b(4)

- We consider the proposed endpoint to be exploratory.

- We consider volume voided to be an important secondary endpoint.

7. Does the Agency agree that a meta-analysis of the secondary variable 'change in the average number of urge incontinence episodes per week' from the Phase 3 trials could be used to support a claim of

b(4)

- No. We reiterate the Division's original position. The most compelling evidence of efficacy would be if each of two Phase 3 trials individually supports the claims of

b(4)

. Details of the meta-analysis are not sufficient and no final agreement on the meta-analysis can be reached at this time.

8. Does the Agency agree to the proposed safety monitoring of the Phase 3 protocols as described in Section 4.7 'Clinical Safety Strategy':

Safety labs
Centralized ECG with manual assessments
Genotyping for CYP 2D6

- Yes, we agree with the proposed safety monitoring, but only if genotyping will be conducted on all subjects in at least one trial. (Note: the sponsor acknowledged that genotyping was planned for all patients in one Phase 3 trial.)

9. Could SP582 be considered one of the major trials that supports approval of the marketing application?

- Study SP582 could be submitted as one of the "pivotal trials" supporting efficacy. However, the lack of statistical evidence for the incontinence endpoint for the 8mg dose will be a major review issue. Overall, we prefer your plan of conducting two additional Phase 3 trials.

10. Does the Agency agree that the following exposures are sufficient for marketing application? (note- exposures appear in background package on pages 13 and 91.)

- Yes, provided the 6-month and 12-month exposure data is at the 8mg dose or greater.

11. Does the Agency agree to the following dosing for the open-label trials: All subjects from the double blind phase initially receive open label fesoterodine hydrogen fumarate 8mg. In the event of undesirable antimuscarinic side effects, a dose reduction to 4mg is possible?

- Yes, we agree to the proposed dosing regimen in the open-label trials. We also accept your proposal to add naïve patients to extension trial SP669.

Additional comments:

Chemistry

- Chemistry issues will be addressed in a separate meeting.

Clinical Pharmacology

- We recommend that the sponsor submit details of Population-PK measurements.
- The Division inquired as to the reason for repeating the food-effect study. The sponsor clarified that the food effect study will be repeated due to a formulation change.
- The Division stated that a bridging study would be needed if the formulation used in the Phase 3 pivotal trials differed from the to-be-marketed formulation.
- The Division noted that the formulation history was not clear and additional clarification should be submitted by sponsor for review.
- The Divison inquired if the sponsor was considering development of an IV/IVC model.

Biometrics

- The co-variates to be used in the statistical model were not defined.
- In case of non-linearity of the efficacy data, the sponsor should consider a non-parametric approach for the analysis.
- The exact method for calculating the treatment differences and the deltas should be provided.

Clinical

- There does not appear to be any specific preclinical data that would support the requirement to include contraception use as an entry criterion for the Phase 3 trials. The Division recommends that this limitation be removed to avoid a similar limitation in labeling.
- b(4)
- The Division encourages the sponsor to enroll as many urgency incontinent patients as possible (the more urge incontinence episodes the better) in the Phase 3 trials.
- If patients with prolonged QT intervals are excluded from Phase 3 trial participation, will such a contraindication be required in labeling? The sponsor may consider screening out extreme cases only.
- Neither the the treatment response scale nor the urgency-severity scale appears adequately validated. The sponsor indicated that they are no longer proposing the treatment response endpoint

QT interval

- Preclinical data indicates a signal for QT prolongation and that a definitive QTc clinical trial is warranted. Sponsor plans to submit a study protocol for such a study by September, 2003. The Division recommends that such a protocol include the following design elements:
  - a placebo control
  - an active positive control to assess assay sensitivity
  - a crossover design
  - inclusion of both genders
  - inclusion of OAB patients if possible; if not, inclusion of demographically-matched subjects
  - repeated dosing to steady state
  - assessment of QT interval at maximum fesoterodine plasma concentration and accounting for AUC
  - use of at least 2 different fesoterodine doses, the higher of which should produce exposures that exceed those expected in a poor CYP 2D6 metabolizer on 400mg of ketoconazole daily (e..g. the "worst case scenario" likely to be encountered in clinical practice)

- use of various methods of corrections, including consideration of the Holter bin method.
- inclusion of a comparator would be at the discretion of the sponsor. No claims, however, could be made based on comparator results.

Action items:

- Minutes will be provided to the sponsor within 30 days
- Sponsor will submit final Phase 3 protocols for agency review
- Sponsor will request an additional End of Phase 2 meeting to specifically discuss CMC requirements.

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

/s/

Mark S. Hirsch
7/16/03 04:36:40 PM
I concur.

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

/s/

Mark S. Hirsch
8/11/05 06:43:33 PM

IND 51,232: Meeting minutes for July 18, 2005 Pre-NDA meeting

Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July , 2005

To: Alan Blumberg, Ph.D., Sr. Director, Regulatory Affairs

Company: Schwarz Pharma

Fax number: 919-767-2570

Phone number: 919-767-2513

From: Jean Makie

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: IND 51,232: Minutes for the 7/18/05 Pre-NDA meeting are attached

NOTE:

Document to be mailed: **YES** **NO**

IND 51,232: Meeting minutes for July 18, 2005 Pre-NDA meeting

Meeting Minutes

IND: 51,232: **Sponsor**: Schwarz Biosciences

Meeting: Type B Pre-NDA

Drug: Fesoterodine (SPM 8272) **Indication:** Overactive bladder

Date: July 18, 2005 **Time**: 11:00 AM to 12:00 PM

Location: Parklawn Building, Conference Room C

FDA Attendees:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Daniel Davis, M.D., Medical Officer, DRUDP

Laurie McLeod, Ph.D., Toxicology Reviewer, DRUDP

Jean Salemme, Ph.D, Chemistry Reviewer, DRUDP

Julie Bullock, Ph.D., Clinical Pharmacology and Biopharmaceutics, DRUDP

Mahboob Sobhan, Ph.D., Biostatistics Reviewer, DRUDP

Jean Makie, M.S., R.D., Sr. Project Manager, DRUDP

Industry Attendees

Christoph Arth, Ph.D., Pharmaceutical Analysis

Alan Blumberg, PhD, Regulatory Affairs, USA

David Dobrowski, B.S., Regulatory Affairs, USA

Hans-Theo Forst, PhD, Biostatistics, Germany

Brian Kilgallen, M.S., Biostatistics, USA

Cornelia Haag-Molkenteller, M.D., Ph.D., Vice President Therapeutic Area Urology, Germany

Ute Massow, PhD, Therapeutic Area Urology, Germany

Richard Sachse, MD, Clinical Pharmacology, Germany

Ute Scharfenecker, PhD, Pharmacokinetics/ADME, Germany

Andrea Schütz, International Project Management, Germany

Chip Sherrill, Medical Writing, USA

Background: The Sponsor requested this Type B, Pre-NDA meeting on May 12, 2005. On May 19, 2005, the Sponsor submitted the following questions in their briefing package to the Division. The Division's preliminary draft responses were faxed to the Sponsor on July 14, 2005. Additional discussion held during the meeting is also summarized below under "Sponsor Response," and/or "Division Comments."

Sponsor's Questions and Issues for discussion

1. In total, approximately 581 subjects were exposed to fesoterodine 8mg by the time of the original NDA safety data cut-off (May 9 2005): 457 for ≥6 months and 124 for ≥12 months. Does the Agency agree that the number of exposed patients for 6 and 12 months is sufficient for filing the initial NDA? For the 4 month Safety Update, Schwarz will submit data on 504 subjects exposed for 6 months and 332 subjects exposed for 1 year. We propose to provide the same displays, tables, figures, listings and required CRFs as those provided in the initial NDA submission Safety Analysis. Is this acceptable to the Division?

Long-term Fesoterodine Exposures (8mg)		
	NDA Submission	**120-day Safety Update**
≥ 6months	457	504
≥ 12months	124	332

Division Response: Yes to both questions.

Sponsor Response: The Sponsor had no additional comments or questions.

2. Does the Agency concur with our pediatric request of a partial waiver for age groups 0–___ years and a deferral for ages____ years pending approval of the NDA? (for details see Attachment 1) Does the Agency agree that no juvenile toxicology would be necessary prior to conducting pediatric studies? Prior to implementing the pediatric program a teleconference or meeting will be requested in order to gain further clarity on protocol design and outcomes. b(4)

Division Response: Yes, the Division concurs with your proposed request for a partial waiver and deferral, however, the age range for the partial waiver request should be changed to up to 5 years when submitted in the original NDA. Refer to 21 CFR 201.57(f)(9), which defines the pediatric population as birth to 16 years. For pediatric studies under PREA or for a Written Request (WR), the age can be extended up to 18 years at the discretion of the Division. In this case, however, it would seem appropriate to include patients up thru 16 years of age.

From a nonclinical perspective, we also recommend a juvenile animal study be conducted prior to conducting pediatric studies and recommend that this protocol be submitted for review by the Division prior to initiation of the study.

Sponsor Response: The Sponsor agreed with the recommendations.

3. Is the Agency willing to assess a proposal for an indication statement "for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency" during the NDA review?

   Division Response: Yes- see our comments from the EOP2 meeting minutes. To support this indication, you will need substantial evidence of efficacy for both micturition frequency and urge incontinence.

   Sponsor Response: The Sponsor agreed with the recommendations.

4. Does the Agency agree with the designated efficacy and safety pools of patients, and the proposed analyses as described in the ISAP? (for details see "Integrated Statistical Analysis Plan" in Attachment 3)

   Division Response: No. For efficacy, pooling of the European and U.S. trials is acceptable only as an exploratory analysis. The most compelling evidence of efficacy will be if each of the two Phase 3 trials individually support the claims of micturition frequency and urge incontinence. If the evidence is less robust than that, it will be a review issue. For safety, we request one additional safety pool to include only the two pivotal Phase 3 studies.

   Sponsor Response: The Sponsor agreed with the recommendations.

5. Does the Agency agree that display of QTc results in patients for safety ECG data using the Fridericia and Bazett formulas will be sufficient?

   Division Response: Yes. For additional information on submitting ECG data for QTc, please refer to the finalized ICH E14 guidance entitled "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."

   Sponsor Response: The Sponsor had no additional comments or questions.

6. Does the Agency agree with the marked abnormalities for clinical laboratory measurements, vital signs and ECG? (for details see applicable sections of the "Integrated Statistical Analysis Plan" [section 3.3.6 "Vital signs," section 3.3.7 "ECG data," and section 6.1 "Harmonized lab normal ranges and marked abnormalities"] in Attachment 3 of the meeting package)

   Division Response: No. For Hgb and Hct, the > the upper limit of normal (ULN) value should serve as the "markedly abnormal" value. We recommend that the markedly abnormal values for the following lab parameters be changed as follows:

   - **Potassium – change 6.0 to 5.7**
   - **AST/ALT and alkaline phosphatase – change >3.0 x ULN to >2.5 x ULN**
   - **CK – change 1000 to 500**

   For ECG, you should define "markedly abnormal" for parameters other than the QT interval (e.g., other intervals, other arrhythmias).

Sponsor Response: The Sponsor requested clarification on the following issues:

- For Hgb and Hct, the Sponsor asked if they should submit all values above the ULN as real values, not percent greater than the ULN.

  Division Response: Yes, submit all values above the ULN as real values, not percent greater than the ULN.

- For ECGs, the Sponsor asked the Division to clarify which additional intervals should be assessed and submitted.

  Division Response: The Division stated that "markedly abnormal" parameters other than the QT interval would include the usual medical monitoring of irregularities and/or adverse side effects consistent with increased amounts of anticholinergics, such as tachycardia and atrial arrhythmias.

7. We are submitting Case Report Forms (CRFs) for deaths and dropouts due to AEs only for subjects with overactive bladder [redacted] b(4)
   . Does the Agency agree with this proposal?

   Division Response: No. You should also include CRFs for patients with SAEs that did not result in discontinuation. Also, you should include CRFs for all deaths, SAEs and dropouts due to AEs, including healthy subjects and renally and hepatically-impaired subjects on fesoterodine.

   Sponsor Response: The Sponsor requested clarification on the following issue:

   - Should we submit the CRFs for subjects who received fesoterodine or should we submit CRFs for all subjects (fesoterodine, placebo, and comparator)?

     Division Response: The Division stated that the Sponsor should submit CRFs for subjects who received fesoterodine in Phase 1, 2 and 3 trials.

8. Does the Agency agree that, in principle, the clinical development program as presented in the Table of All Clinical Trials and that the placement of the trials within the Table of all Clinical Trials are acceptable? (for details see section 4.4 of the meeting package)

   Division Response: Yes. Refer also to the Division's response to Question 11 which pertains to necessary information on CYP2D6 metabolism. b(4)

9. Schwarz intends to write narratives for all deaths and all SAEs for subjects on fesoterodine regarded as [redacted] by the investigator. Is this acceptable to the FDA?

   Division Response: No. Submit narratives for all deaths and SAEs for subjects on fesoterodine from all trials including those considered by the investigator as related and those considered not related to trial medication.

   Sponsor Response: The Sponsor requested clarification on the following issue:

   - Should we submit narratives for subjects who received fesoterodine or should we submit CRFs for all subjects (fesoterodine, placebo, and comparator)?

Division Response: The Division stated that the Sponsor should submit narratives for subjects who received fesoterodine in Phase 1, 2 and 3 trials.

10. We will also provide narratives for dropouts due to nonserious AEs deemed related by the Investigator due to increases in liver function tests, ECG changes, tachycardia, constipation, or increased residual urine, and any QTcB increases of 60ms over baseline or QTcB above 500ms. Is this sufficient?

    Division Response: No. Please also provide narratives for dropouts due to ophthalmologic adverse events.

    Sponsor Response: The Sponsor requested clarification on the following issue:

    - Should we submit narratives for dropouts due to nonserious AEs deemed related to fesoterodine or regardless of reported relatedness by the Investigator?

      Division Response: The Division stated that the Sponsor should submit narratives for all dropouts due to nonserious AEs regardless of reported relatedness to fesoterodine by the Investigator in Phase 1, 2 and 3 trials.

11. Are the data presented adequate to judge the potential for drug-drug interactions? (for details see section 4.2.1.10 of the meeting package)

    Division Response: Yes. However, despite the Division's previous recommendations, you have not conducted a CYP2D6 inhibition study. Instead, you propose to use the results from CYP2D6 genotype studies to address the extent of drug inhibition by CYP2D6 inhibitors. Your proposal is scientifically sound, but we remind you that appropriate genotype determinations are critical for identifying metabolic polymorphism of CYP2D6 and to accurately classify subjects as extensive/poor metabolizers (EMs/PMs). Thus, you should submit to the NDA the methodology (genotype/phenotype) and specific alleles (as patient line listings) used to determine CYP2D6 EMs/PMs for all Phase 1 studies where EMs and PMs have been enrolled. This will be a review issue.

    Sponsor Response: The Sponsor agreed with the recommendations.

12. Is it sufficient to present pooled safety data for the 120-day safety update or do we need to provide interim trial reports as well?

    Division Response: For the ongoing safety studies, this is acceptable. For any new studies, interim trial reports are requested.

    Sponsor Response: The Sponsor agreed with the recommendations.

13. Schwarz will submit SAS datasets for each of the two Phase 3 studies and therefore, does not intend to submit Case Report Form (CRF) tabulations (patient line listings) as part of the eCTD format NDA. Does the Agency agree with this approach?

    Division Response: For efficacy parameters, this is acceptable. For all safety parameters, we request CRF tabulations (patient line listings).

    Sponsor Response: The Sponsor requested clarification on the following issue:

- Should we submit CRF tabulations for only subjects in Phase 3 studies?

  Division Response: The Division stated that the Sponsor should initially submit CRF tabulations for subjects who were enrolled in large Phase 2 and all Phase 3 studies. Additional CRF tabulations for subjects who were enrolled in Phase 1 studies may be requested during the review cycle.

14. Schwarz plans to submit SAS datasets for the carcinogenicity studies but not for any additional nonclinical studies. Does the Agency agree?

    Division Response: We agree to the submission of SAS datasets for the carcinogenicity studies with no such requirement for other nonclinical studies.

    Sponsor Response: The Sponsor had no additional comments or questions.

15. Tissue distribution studies in pigmented mice and rats following single oral administration of 5 mg/kg of [^{14}C]-fesoterodine and in dogs following single oral administration of 0.5 mg/kg of [^{14}C]-fesoterodine indicated that levels of drug-related material decreased more slowly in the eye compared to other tissues. Ophthalmic and histopathological examinations in rodents were normal. In the dog reversible mode-of-action-related effects were observed. Schwarz believes that given the lack of adverse effects of fesoterodine on the eye in rodents and dogs following long-term exposure no further studies are required. Does the Agency concur? (for details see Attachment 2).

    Division Response: At this time, the Division's preliminary response is that no additional nonclinical ocular toxicity testing is required. From a Clinical perspective, we have concerns related to dry eyes and conjunctivitis reported in dogs and humans. Sponsor was asked whether specific human studies have been conducted to assess ocular adverse events. This could be a significant safety concern for the NDA. The sponsor was informed that an internal consult from Opthalmology was requested to determine whether any additional preclinical or human investigations are deemed necessary.

    Sponsor Response: The Sponsor requested clarification on the following issue:

    - The Sponsor stated that specific human studies were not conducted to specifically assess ocular adverse events. The Sponsor asked if the Division believed additional studies would be necessary to include in the NDA or as a possible post-marketing commitment?

      Division Response: The Division stated that the recommendations from the ophthalmologic consult remain pending. At this time, the need for additional trial(s) is not known, however, the Division committed to provide the Sponsor with recommendations as soon as available.

    Sponsor Response: The Sponsor stated that they believe the severity of the reported ocular events is inaccurately elevated due to changes in the MeDRA coding for dry eyes between the previous MeDRA version 6.0 and the current

MeDRA version 7.0, which now uses the MeDRA preferred term of 'Keratokonjunctivitis sicca.' The Sponsor will address these issues in the NDA submission and will await further recommendations from the ophthalmology consult.

16. Stability data of fesoterodine SR tablets in the NDA submission will consist of the following: 24 month data on 3 batches of each dosage strength (4mg and 8mg) manufactured at the Zwickau site ( ) as supportive stability data; 6 month data on 3 batches of each dosage strength (4mg and 8mg) manufactured at the Seymour site (as primary stability data. During the review process we propose to submit data from the 9 month and 12 month test points for the batches manufactured at the proposed commercial drug product manufacturing site (Seymour) in April, 2006. Does the agency concur with this proposed stability strategy? b(4)

Division Response: Because of multiple changes involved during the clinical development program in the to-be-marketed product, the supportive stability may not contribute to establishing the expiration date of the drug product. The expiration date for the proposed drug product will be based mainly on the data provided for the primary batches manufactured at the Seymour site.

The Division agrees to review the additional stability data, to 12 months for the one batch of each strength tablet, and to 9 months for the additional two batches of each strength tablet, if these data are submitted no later than three months before the goal date of the NDA.

Sponsor Response: The Sponsor requested clarification on the following issue:

- The Sponsor stated that they expect to have 12 months of stability data in July, 2006. If the bioequivalence data are acceptable, would the combined data be adequate to support a 24-month expiry?

Division Response: No. These data would only support an 18-month stability.

ADDITIONAL CMC COMMENTS:

1. **For the " intermediate to be acceptable as a starting material, complete CMC information for the starting material should be provided, either in the NDA or in a DMF with a Letter of Authorization. Additionally, the sponsor is required to commit to notify the Agency, by a supplement to the NDA, if either the supplier of the starting material changes or any manufacturing changes are made to the approved supplier's manufacturing process.** b(4)
2. **The drug substance specification indicates that the limit parts per million (ppm), for the residual solvent than the 5000 ppm level recommended in ICH Q3C guidance. The limit should be less than 5000 ppm.**
3. **Data should be provided to demonstrate that the drug substance to be used in the commercial product is equivalent to the drug substance used in the clinical as well as nonclinical batches with respect to the impurity profile, and particle size distribution.** b(4)

4. **Dissolution profile data for drug product lots should be reported as individual values, rather than as the range and mean.**

   Sponsor Response: The Sponsor agreed with the recommendations. The Sponsor stated, however, that the drug substance limits in the batches from the Phase 1, 2, and 3 studies ——— the 5000 ppm. These data will be submitted in the NDA. b(4)

   Division Response: The Division stated this will be a review issue.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

1. **The results of trial SP842 must be included in the original NDA. Document in the NDA that the clinical trial formulation is equivalent to the to-be-marketed formulation.**
2. **For each study, clearly define the formulation or formulations used in that trial.**
3. **Ensure that the food-effect information is representative of the final to-be-marketed formulation.**
4. **Consider developing an IVIVC for this product. If this has been attempted, submit with the NDA. Refer to the Guidance Document entitled "Extended release oral dosage forms: Development, evaluation, and application of In Vitro/In Vivo correlations" (http://www.fda.gov/cder/guidance/1306fnl.pdf).**
5. **Provide in vitro dissolution data with different pH media.**
6. **In the NDA, provide full genotype and/or phenotype information for the Phase 1 trials that enrolled extensive and poor metabolizers of CYP2D6.**
7. **The robustness of the modified release formulation when concomitantly administered with alcoholic drinks should be considered.**
8. **The genotype information from the Phase III trials (if available) may be voluntarily submitted to the Voluntary Genomics Data Submission group (VGDS) at the FDA (Attn: Allen Rudman, email rudman@cder.fda.gov)**

Sponsor Response: The Sponsor agreed with recommendations. The Sponsor also responded that they will be able to provide in vitro dissolution data for pH range of 1-7.

Division Response: The Division stated that this was acceptable.

ADDITIONAL PHARMACOLOGY/TOXICOLOGY COMMENTS:

1. **A comprehensive analysis of human metabolite blood levels was not available for review. A major human metabolite is now considered to be one that comprises greater than 10% of parent blood levels. When the human data is available, it should be demonstrated that all major human metabolites have been adequately covered in chronic toxicity, genotoxicity, carcinogenicity, and reproductive studies.**

2. **Document that all impurities greater than .15% of the final to-be-marketed product have been qualified in nonclinical studies.**

   Sponsor Response: The Sponsor agreed with the recommendations.

Executive CAC amendment to minutes
Date of Meeting: March 12, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abby Jacobs, Ph.D., HFD-540, Alternate Member
C. Joseph Sun, Ph.D., HFD-570, Alternate Member
Alex Jordan, Ph.D., Team Leader
Laurie McLeod-Flynn, Ph.D., Presenting Reviewer

Author of Draft: Laurie McLeod-Flynn

IND # 51232
Drug Name: Fesoterodine
Sponsor: Schwartz Biosciences, Inc.

On March 12, 2002, CAC stated that it could not concur that a maximally tolerated dose had been achieved in the rat carcinogenicity study. However, the committee stated that it could concur if (1) an increase in mortality or a biologically significant dose related decrease in body weight was demonstrated in both male and female rats during the course of the *ongoing* carcinogenicity study or (2) an increase in mortality or a biologically significant dose related decrease in body weight was demonstrated in both male and female Sprague-Dawley rats at or near 60 mg/kg/day (oral gavage) in a new dose ranging study that evaluates the dose response at and above 60 mg/kg/day.

On July 3, 2002, Schwartz Biosciences responded by providing an interim analysis (53 week data tabulated below) of their rat carcinogenicity assay in support of 60 mg/kg/day being a maximally tolerated dose in both male and female rats.

Mortality	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60	0	5	15	45/60
Week 8	0	0	0	0	0	0	0	0
Week 17	0	0	0	0	0	0	0	0
Week 25	0	0	0	0	0	0	0	0
Week 33	0	0	2	0	0	0	2	0
Week 43	2	0	2	2	0	0	2	2
Week 53	4	4	6	10	4	0	2	2

Body wt.	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	15	45/60 (%cont.)	0	5	15	45/60 (%cont.)
Week 13	455.6	461.0	457.5	444.4 (-2.5%)	281.7	282.4	289.4	284.7 (+1.1%)
Week 29	521.8	528.8	522.4	499.4** (-4.3%)	316.7	314.9	319.9	309.7 (-2.2%)
Week 33	547.0	546.6	541.9	512.7** (-6.3%)	325.3	326.9	331.2	314.1 (-3.4%)
Week 43	564.5	569.8	560.8	520.9** (-7.7%)	336.9	336.1	341.1	317.3 (-5.8%)
Week 53	569.4	580.4	569.0	525.3** (-7.7%)	349.7	348.2	353.1	326.0 (-6.8%)

CAC concurs that a maximally tolerated dose has been achieved for both males and females in the rat carcinogenicity study.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\

/Division File, HFD-580
Alex Jordan/Team leader, HFD-580
Laurie McLeod-Flynn/Reviewer, HFD-580
Jennifer Mercier/CSO/PM, HFD-580
/ASeifried, HFD-024

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

/s/

Joe Contrera
8/28/02 03:05:47 PM