

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-807

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-807

SUPPL #

HFD # -150

Trade Name Soltamox Oral Solution

Generic Name tamoxifen citrate

Applicant Name Savient Pharmaceuticals

Approval Date, If Known October 29, 2005

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)(2)

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.

The applicant relied on the safety and efficacy data submitted for the reference listed drug (NDA 17-970) for Nolvadex. The sponsor acknowledges that only a bioequivalence study was conducted and submitted with this application to establish that the tablet and oral solution formulations are equivalent.

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?

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?

No

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# 17-970

Nolvadex (tamoxifen citrate) Tablets

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

YES
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Christy Cottrell
Title: Consumer Safety Officer
Date: October 31, 2005

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Acting Division Director

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

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

/s/

Christy Cottrell
10/31/2005 02:41:16 PM

Robert Justice
10/31/2005 05:41:24 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-807 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 1-12-05 Action Date: 11-12-05 (PDUFA date)

HFD-150 _____ Trade and generic names/dosage form: Soltamox (tamoxifen citrate) Oral Solution

Applicant: Savient Pharmaceuticals Therapeutic Class: 3 S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 4

Indication #1: Metastatic Breast Cancer: Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from tamoxifen citrate therapy.

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

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Other: _____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

Attachment A

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

Indication #2: Adjuvant Treatment of Breast Cancer: Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with four or more positive axillary nodes.

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.

The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

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

Yes: Please proceed to Section A.

No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

Formulation needed

Other: _____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

Attachment A

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

Indication #3: Ductal Carcinoma in Situ (DCIS): In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see BOXED WARNING at the beginning of the label). The decision regarding therapy with tamoxifen for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen therapy.

Current data from clinical trials support five years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

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

Yes: Please proceed to Section A.

No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

Attachment A

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

Indication #4: Reduction in Breast Cancer Incidence in High Risk Women: Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality (see BOXED WARNING at the beginning of the label).

Tamoxifen citrate is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer $\geq 1.67\%$, as calculated by the Gail Model.

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

Yes: Please proceed to Section A.

No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager

cc: NDA 21-807
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Christy Cottrell
9/28/2005 03:32:30 PM

From: Cottrell, Christy
Sent: Wednesday, June 15, 2005 10:40 AM
To: 'bkundu@savientpharma.com'
Subject: FW: NDA 21-807 for Soltamox
Briti,

Can you also give us a status update on your submission of the Gail risk calculator(s)?

Thanks,
Christy

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

From: Cottrell, Christy
Sent: Wednesday, May 18, 2005 9:49 AM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807 for Soltamox

Briti,

The approved labeling for Nolvadex includes a Gail risk calculator for predicting risk. You will need to submit a similar calculator to accompany the labeling for Soltamox. Both high-tech and low-tech versions are required (i.e., a computer disk is acceptable, but a hand-held calculator must also be submitted for those who do not have access to a computer). Please make certain that your calculators incorporate any recent updates that have been made to the innovator's calculators (i.e., that they calculate the correct estimation of risk for all demographics). Please submit these risk calculators ASAP so we may review them.

Thanks,
Christy

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/s/

Christy Cottrell
6/15/05 11:39:21 AM
CSO

From: Cottrell, Christy
Sent: Tuesday, June 14, 2005 2:44 PM
To: 'Kundu, Briti'
Subject: RE: NDA 21-807: request for CMC information
Briti,

I'm just following up on a couple of items from your April 25th email (below).

1. With regard to your response to item #3, please add these to the specification table.
2. With regard to items #6 and #7, we haven't yet received a response from you. Please let us know when we can expect your response.

Thanks,
Christy

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

From: Kundu, Briti [mailto:bkundu@savientpharma.com]
Sent: Monday, April 25, 2005 7:43 PM
To: Cottrell, Christy
Subject: RE: NDA 21-807: request for CMC information

Christy,

Thank you for e-mailing the CMC questions. A significant amount of information, required to respond to the questions, was already included in the application. I have simply pointed and referenced the sections and statements. I have the following comments/responses in this color to the questions from the CMC reviewer. .

Briti,

Please refer to your pending NDA 21-807 for Soltamox. See below for a request for additional information from the CMC reviewer:

Please provide the following:

For the drug substance:

1. Acceptance criteria for the following parameters of the two non-compendial flavoring agents, aniseed and licorice: grade, chemical specification and microbiological specification.

The information regarding the flavors is included in the 'drug product' section of the CMC.

These two flavors are received from [REDACTED] These flavors are accepted based on the specifications provided by [REDACTED] They define the grade of the flavors as 'natural flavoring', 'does not contain any toxic ingredients' and

certify that they comply with the FAO/WHO directives . The certificates of analyses of the flavors from [REDACTED] on NDA pages, pages 4- 375, 4-377, 4-379, 4-381, 4-383 provides the grade and specifications.

The Rosemont analytical methods for these two flavors on NDA pages 4-46 to 4-61 describes the acceptance specifications for both flavors. I am providing a summary of the tests that are performed:

Licorice : [NDA pages 4-46 to 4-53]

1. Check lot information
2. Check test information
3. Check manufacturer's certificate of analysis
4. Description
5. Odor
6. Specific gravity , [REDACTED] NDA page 4-51
7. [REDACTED] , NDA page 4-50

Aniseed: [NDA pages 4-54 to 4-62]

1. Check lot information
2. Check test information
3. Check manufacturer's certificate of analysis
4. Description
5. Odor
6. Specific gravity , [REDACTED] NDA page 4-59
7. [REDACTED] NDA page 4-60
8. [REDACTED] NDA pages 4-61

The Rosemont test results of these flavors are on NDA pages 4-374, 4-376, 4-379 and 4-380

2. Batch analysis data provided do not clearly specify the impurities measured in each batch. Please provide the amount of each specified and unknown impurity in each batch and we recommend that you continue to report these data in subsequent COAs.

If the reference in point no. 2 is made to the active pharmaceutical ingredient/drug substance (API), then please note that the API is received from the manufacturer [REDACTED] (DMF [REDACTED]) and are accepted on the basis of their certificate of analysis and Rosemont performs ID, assay and description of each lot of API. [REDACTED] notes the related compounds and [REDACTED] unknown impurity in their specifications on the certificate of analysis for each of their batches. Rosemont performs full USP testing on every [REDACTED] lot [NDA page 4-7]. Detailed information regarding the specified and unknown impurities of the lots received from [REDACTED] can be found on their certificates of analyses [NDA pages 4-12, 4-13; 4-15, 4-16; 4-18,4-19; 4-21,4-22 and 4-24, 4-5. The FULL USP test results, performed by

Rosemont are included in NDA page 4-27. We believe that these controls for the API are adequate to assure the quality of the finished drug product SOLTAMOX™.

For the drug product:

3. A limit for total impurities in your drug product release specifications.

This information is on NDA page 4-189: [REDACTED] and total unknown impurities is [REDACTED]

4. Test data for extractables and leachables from container closure system.

The container is Type III amber GLASS bottles and the complete technical package from the manufacturer included in the NDA [page 4-103 to 4- 131] noted testing for [REDACTED]. The manufacturer of the closure certifies on page 4-155 that the [REDACTED] complies with 21CFR177.1520 ([REDACTED]). Let us know whether the reviewer still needs the information noted above.

5. A table listing the controls of critical manufacturing steps and intermediates, and the specifications associated with these in-process controls.

The method of manufacturing (MOM), detailed of which are in the schematic and the master formula, starting on NDA page 4-66, is very simple and notes addition and dissolution of ingredients. [REDACTED]

6. Please propose a stability protocol along ICH recommended test stations. The protocol submitted was not performed in this way.

Rosemont has a [REDACTED] stability protocol in place. We will evaluate the protocol for ICH compliance and forward the document.

7. Please revise the storage temperature for drug product to "Store at 20°-25°C (68°-77°F). Do not store above 25°C (77°F)."

The first part of the recommendation is being evaluated from historical storage and marketing aspects. We agree to include the second statement.

Please let us know whether these responses are satisfactory to the reviewer.

Regards,

Briti

From: Cottrell, Christy
Sent: Tuesday, May 31, 2005 11:51 AM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807 for Soltamox
Briti,

Our DMETS has requested that you submit the calibrated cup to be distributed with Soltamox for review. Please send it to my attention.

Thanks,
Christy Cottrell
Project Manager
Division of Oncology Drug Products, FDA

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

/s/

Christy Cottrell
5/31/05 02:45:32 PM
CSO

From: Cottrell, Christy
Sent: Wednesday, May 18, 2005 9:49 AM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807 for Soltamox
Briti,

The approved labeling for Nolvadex includes a Gail risk calculator for predicting risk. You will need to submit a similar calculator to accompany the labeling for Soltamox. Both high-tech and low-tech versions are required (i.e., a computer disk is acceptable, but a hand-held calculator must also be submitted for those who do not have access to a computer). Please make certain that your calculators incorporate any recent updates that have been made to the innovator's calculators (i.e., that they calculate the correct estimation of risk for all demographics). Please submit these risk calculators ASAP so we may review them.

Thanks,
Christy

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/s/

Christy Cottrell
5/18/05 11:11:30 AM
CSO

From: Cottrell, Christy
Sent: Monday, April 25, 2005 2:40 PM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807: request for CMC information
Briti,

Please refer to your pending NDA 21-807 for Soltamox. See below for a request for additional information from the CMC reviewer:

Please provide the following:

For the drug substance:

1. Acceptance criteria for the following parameters of the two non-compendial flavoring agents, aniseed and licorice: grade, chemical specification and microbiological specification.
2. Batch analysis data provided do not clearly specify the impurities measured in each batch. Please provide the amount of each specified and unknown impurity in each batch and we recommend that you continue to report these data in subsequent COAs.

For the drug product:

3. A limit for total impurities in your drug product release specifications.
4. Test data for extractables and leachables from container closure system.
5. A table listing the controls of critical manufacturing steps and intermediates, and the specifications associated with these in-process controls.
6. Please propose a stability protocol along ICH recommended test stations. The protocol submitted was not performed in this way.
7. Please revise the storage temperature for drug product to "Store at 20°-25°C (68°-77°F). Do not store above 25°C (77°F)."

If you have any questions, feel free to call me at (301) 594-5778.

Thanks,
Christy Cottrell
Consumer Safety Officer
Division of Oncology Drug Products, FDA

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

/s/

Christy Cottrell
4/25/05 02:42:07 PM
CSO

Cottrell, Christy

From: Turner, Tara
Sent: Tuesday, April 12, 2005 4:15 PM
To: Cottrell, Christy
Subject: FW: DFS Email - N 021807 N 000 AR 12-Jan-2005 - Forms



090014648051
529.pdf (88 KB)

Hi Christy,

Thanks for your consult request to review the Medication Guide for Soltamox (tamoxifen citrate) Oral Solution. Since this is a 505(b)(2) application, the review division will need to review the Medication Guide and ensure that it matches the Medication Guide of the referenced product, Nolvadex (tamoxifen citrate) Tablets, with the exception of the dosing instructions since this is a different dosage form. The same holds true for generic products. DSRCS does not provide reviews of patient information for either of these application types.

Please let me know if you have any questions or concerns.

Thanks,
Tara

Tara P. Turner, Pharm.D.
LT, USPHS
Division of Surveillance, Research, and Communication Support
Office of Drug Safety
Food and Drug Administration
Parklawn Room 6-22 (HFD-410)
Phone 301-827-7844; Fax 301-827-7241
E-mail: turnert@cderr.fda.gov

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

From: Kang, Robert
Sent: Tuesday, April 12, 2005 3:43 PM
To: CDER ODS DSRCS CONSULTS
Cc: Turner, Tara
Subject: FW: DFS Email - N 021807 N 000 AR 12-Jan-2005 - Forms

MedGuide review.

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

From: CDERDocAdmin [mailto:CDERDocAdmin]
Sent: Tuesday, April 12, 2005 2:39 PM
To: ODSCONSULTS@CDER.FDA.GOV; DDR_150@CDER.FDA.GOV
Subject: DFS Email - N 021807 N 000 AR 12-Jan-2005 - Forms

Document room update the following:

	Decision Date	Decision Code
	-----	-----
N 021807 N 000 AR 12-Jan-2005	12-Apr-2005	:

Document Type: Forms
Form Group: CONSULT
Form Name: ODS Consult (Except Tradename Reviews)
Submission Description: DSRCS consult for MedGuide

Author(s)/Discipline(s)

1. Christy Cottrell, CSO

Signer(s)

1. Christy Cottrell
DDR: Please process this outgoing consult to HFD-400 (ODS- DSRCS). The labeling is
available in the EDR.
12-Apr-2005

Supervisory Signer(s)

1. Christy Cottrell
DDR: Please process this outgoing consult to HFD-400 (ODS- DSRCS). The labeling is
available in the EDR.
12-Apr-2005

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

DATE RECEIVED: April 12, 2005	DESIRED COMPLETION DATE: July 12, 2005	ODS CONSULT #: 05-0093
DOCUMENT DATE: January 12, 2005	PDUFA DATE: November 12, 2005	

TO: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Christy Cottrell
Project Manager
HFD-150

PRODUCT NAME:
Soltamox™
(Tamoxifen Citrate Oral Solution)
10 mg/5 mL
NDA#: 21-807

SPONSOR:
Savient Pharmaceuticals, Inc.

SAFETY EVALUATOR: Todd Bridges, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Soltamox™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document
2. DMETS recommends implementation of the label and labeling revisions as outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Soltamox™, acceptable from a promotional perspective.

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 9, 2005

NDA #: 21-807

NAME OF DRUG: **Soltamox™**
(Tamoxifen Citrate Oral Solution)
10 mg/5 mL

NDA SPONSOR: Savient Pharmaceuticals, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150), for assessment of the proprietary name, Soltamox™, regarding potential name confusion with other proprietary or established drug names. The container labels, carton and package insert labeling were submitted for review and comment.

PRODUCT INFORMATION

Soltamox™ (NDA 21-807) is a 505(b)(2) application that provides for a new oral solution dosage form of Nolvadex® (tamoxifen citrate) tablets (NDA 17-970). Soltamox™ (Tamoxifen Citrate Oral Solution) is indicated to treat node-positive breast cancer in postmenopausal women, to reduce the risk of invasive breast cancer in women with ductal carcinoma in situ, and to reduce the incidence of breast cancer in women at high risk for breast cancer. The recommended dose is 20 mg to 40 mg per day. Soltamox™ will be available as an oral solution. Each 5 mL of solution will contain 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databasesⁱⁱⁱ for existing drug names which sound-alike or look-alike to Soltamox™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database^{iv} and the data provided by Thomson & Thomson's SAEGIS™ Online Service^v were also conducted. An Expert Panel discussion was

ⁱ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.

^{iv} WWW location <http://www.uspto.gov>.

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

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

1. DDMAC finds the proprietary name, Soltamox™, acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Soltamox™. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified for Soltamox®

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Soltamox	Tamoxifen citrate 15.2 mg/5 mL (equivalent to 10 mg tamoxifen) oral solution	20 mg to 40 mg daily	N/A
Lotemax	Loteprednol etabonate 0.5 % ophthalmic suspension	1-2 drops into affected eye four times daily. initially may increase to 1 drop every hour	L/A
Sporanox	Itraconazole 100 mg capsules 10 mg/ mL injection 10 mg/ mL oral solution	100 mg to 400 mg daily	S/A
Dostinex	Cabergoline 0.5 mg tablets	0.25 mg to 1 mg twice weekly	L/A
Solaraze	Diclofenac sodium 3 % gel	Apply twice daily.	L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

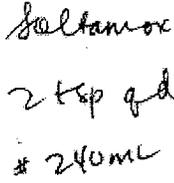
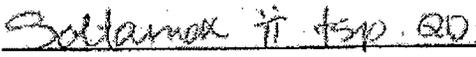
B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered having significant phonetic or orthographic similarities to Soltamox™ were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Soltamox™ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Soltamox™. These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	Soltamox 2 teaspoonful daily Dispense 240 mL
<u>Inpatient RX:</u> 	

2. Results:

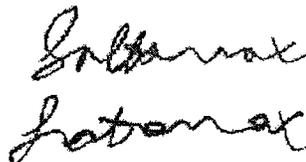
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 9) for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESMENT

In reviewing the proprietary name, Soltamox™, the primary concerns raised were related to look-alike and/or sound-alike confusion with Lotemax™, Sporanox®, Dostinex®, and Solaraze®. Upon further review of the names gathered from EPD, the names Sporanox®, Dostinex®, and Solaraze® were not reviewed further due to a lack of convincing look-alike and sound-alike similarities with Soltamox™ in addition to differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage form.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Soltamox™.

Lotemax™ may look similar to Soltamox™ when scripted. Lotemax™ is a corticosteroid ophthalmic suspension indicated for the treatment of steroid responsive inflammatory conditions and for the treatment of post-operative inflammation following ocular surgery. Lotemax™ is available as a 0.5% suspension in 2.5 mL, 5 mL, 10 mL, and 15 mL containers. The usual dose is one to two drops instilled into the conjunctival sac of the affected eye(s) four times daily. The look-alike similarities between the names can be attributed to shared similar endings, “-emax” vs. “-amox”, which may look-alike when written (see below). Although both names have the upstroke of the letter “t”, Soltamox™ has an additional upstroke letter “l” which helps to differentiate the names from each other when written. The drug names are further distinguished from one another by having different initial letters (“L” vs. “S”). Additionally, Lotemax™ and Soltamox™ do not share any overlapping product characteristics. They differ in indication (ophthalmic inflammation vs. cancer), strength (0.5% vs. 10 mg/5 mL), route of administration (topical vs. oral), dosage form (suspension vs. solution), frequency of administration (four times daily vs. once or twice daily), dose (1 to 2 drops vs. 2 teaspoonful), and size of unit-of-use container (2.5 mL, 5 mL, 10 mL or 15 mL vs. 150 mL). Although Lotemax™ and Soltamox™ differ in strength, the strength may be omitted on a prescription since each drug is available as a single strength. However, a prescription for either medication will likely include the net quantity and a “Sig” stating the dose and frequency of administration which may help to differentiate the two names. Furthermore, a prescriber ordering Lotemax™ will usually indicate the affected eye by inclusion of “OS”, “OD” or “OU” in the directions for use. Overall, different product characteristics such as the dosing interval (QID vs. QD or BID) and orthographic differences in the beginning portion of each name will minimize the potential for confusion and error between Lotemax™ and Soltamox™.



The image shows two handwritten words, 'Soltamox' and 'Lotamax', written in cursive. The 'Soltamox' word has a distinct upstroke on the letter 'l' that is absent in the 'Lotamax' word, which is used to illustrate the visual differences between the two names.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

1 Page(s) Withheld

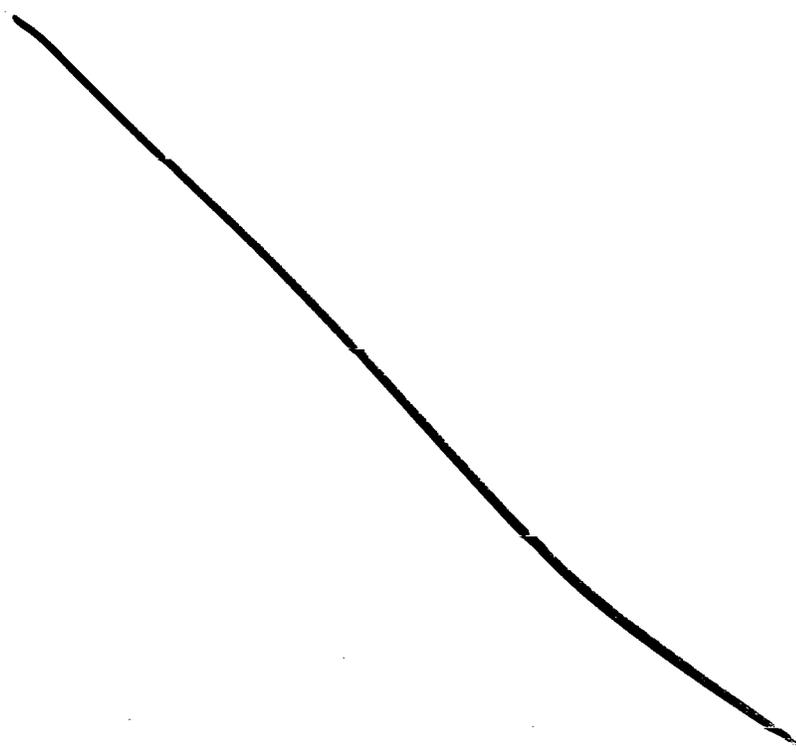
 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1

C. CARTON LABELING



IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Soltamox™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize the potential errors with the use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name, Soltamox™, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith, Project Manager, at 301-827-1998.

Todd Bridges, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Y. Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. DMETS prescription study results for Soltamox™

Outpatient	Voice	Inpatient
Saltamox	Sofomox	Solatamax
Saltamox	Soltamox	Soltamax
Seltamox	Soltamox	Soltamax
Soltamox	Soltamox	Soltamax
Soltamox	Soltamox	Soltamax
Soltamox	Soltavox	Soltamax
Soltamox	Soltimox	Soltamax
Soltamox	Soltomox	Soltamax
Soltamox	Sophomax	Soltamax
Soltamox	Sulfamox	Soltamax
Soltamox	Sulfamox	Soltamax
Soltamox	Zoltamox	Soltamax
Soltamox		Soltamax
Soltanrox		Soltamax
Soltanrox		Soltamax
Sotamox		Soltamax
		Soltamax
		Soltamax
		Soltarmax
		Soltarnax

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/s/

Todd Bridges
6/29/05 09:22:21 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/29/05 11:43:35 AM
DRUG SAFETY OFFICE REVIEWER

From: Cottrell, Christy
Sent: Monday, April 11, 2005 2:16 PM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807
Briti,

Please refer to your pending NDA 21-807 for Soltamox. Below is a request for additional information from the clinical pharmacology reviewer.

Please provide the following information. This will help expedite the review.

TAMOX1 Study

1. Individual raw pharmacokinetic data including demographic information, concomitant medications and individual PK parameters, for the TAMOX1 study. The data should be submitted as sas transport files (*.xpt format).
2. Results from long and short term stability information for bioanalytical plasma samples for TAMOX1.
3. Duration of storage of individual samples for TAMOX1.

CO501 and CO501-2 Studies

1. Results of long and short term stability information for bioanalytical plasma samples for CO501 and CO501-2 studies.
2. Duration of storage of individual samples for CO501 and CO501-2 studies.

If you have any questions, feel free to call me at (301) 594-5778.

Thanks,
Christy Cottrell
Consumer Safety Officer
Division of Oncology Drug Products, FDA

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/s/

Christy Cottrell
4/11/05 02:17:40 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-807

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard, 14th floor
East Brunswick, NJ 08816

Attention: Briti Kundu
Senior Director, Regulatory Affairs

Dear Ms. Kundu:

Please refer to your January 12, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Soltamox™ (tamoxifen citrate) Oral Solution 10mg/5mL.

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 March 13, 2005, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5778.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
3/24/05 12:28:25 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-807

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard, 14th floor
East Brunswick, NJ 08816

Attention: Briti Kundu
Senior Director, Regulatory Affairs

Dear Ms. Kundu:

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:	Soltamox™ (tamoxifen citrate) Oral Solution 10mg/5mL
Review Priority Classification:	Standard (S)
Date of Application:	January 12, 2005
Date of Receipt:	January 12, 2005
Our Reference Number:	NDA 21-807

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 March 13, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 12, 2005.

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 requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

NDA 21-807

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, Room 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, Room 3067
1451 Rockville Pike
Rockville, Maryland 20854

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5778.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Christy Cottrell
3/23/05 11:22:20 AM
Signing for Dotti Pease

Cottrell, Christy

From: Brower, Margaret E
Sent: Tuesday, February 08, 2005 12:14 PM
To: Cottrell, Christy
Cc: Leighton, John K
Subject: Soltamox NDA

Christy,

After looking over the Soltamox submission, it appears that there is no "new" preclinical data for review or for the label. A pharm/tox NDA review will not be necessary. Minor labeling formatting changes may be required.

Thanks
Margot

From: Cottrell, Christy
Sent: Monday, January 31, 2005 2:10 PM
To: 'bkundu@savientpharma.com'
Subject: NDA 21-807
Briti,

Please refer to your pending NDA 21-807 for Soltamox. The Chemistry reviewer has requested the following additional information:

- Please supply a list of manufacturing sites for the drug substance and drug product, sites of release and stability testing, and packaging sites. Please include addresses and CFN numbers.

We must receive this information no later than Monday, February 22, 2005. If you have any questions, feel free to call me at (301) 594-5761.

Thanks,
Christy Cottrell
Project Manager
Division of Oncology Drug Products
FDA
phone: (301) 594-5761
fax: (301) 594-0499
email: cottrellc@cder.fda.gov

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/s/

Christy Cottrell
1/31/05 02:36:39 PM
CSO

**DIVISION OF ONCOLOGY DRUG PRODUCTS
CSO LABELING REVIEW**

NDA: NDA 21-807
DRUG: Soltamox (tamoxifen citrate) Oral Solution
SPONSOR: Savient Pharmaceuticals
DATE OF SUBMISSION: January 12, 2005 (AR)

BACKGROUND:

This 505(b)(2) NDA provides for an oral solution formulation of tamoxifen citrate.

I compared the proposed package insert and Medication Guide for Soltamox to the most recently approved package insert for the reference drug, Nolvadex (tamoxifen citrate) Tablets (NDA 17-970/SLR-053) dated March 17, 2005. The Gail risk assessment tools submitted as part of the Soltamox labeling were reviewed by Dr. Ramzi Dagher.

The proposed labeling is identical to the labeling for the reference drug, except where outlined below.

DISCUSSION:

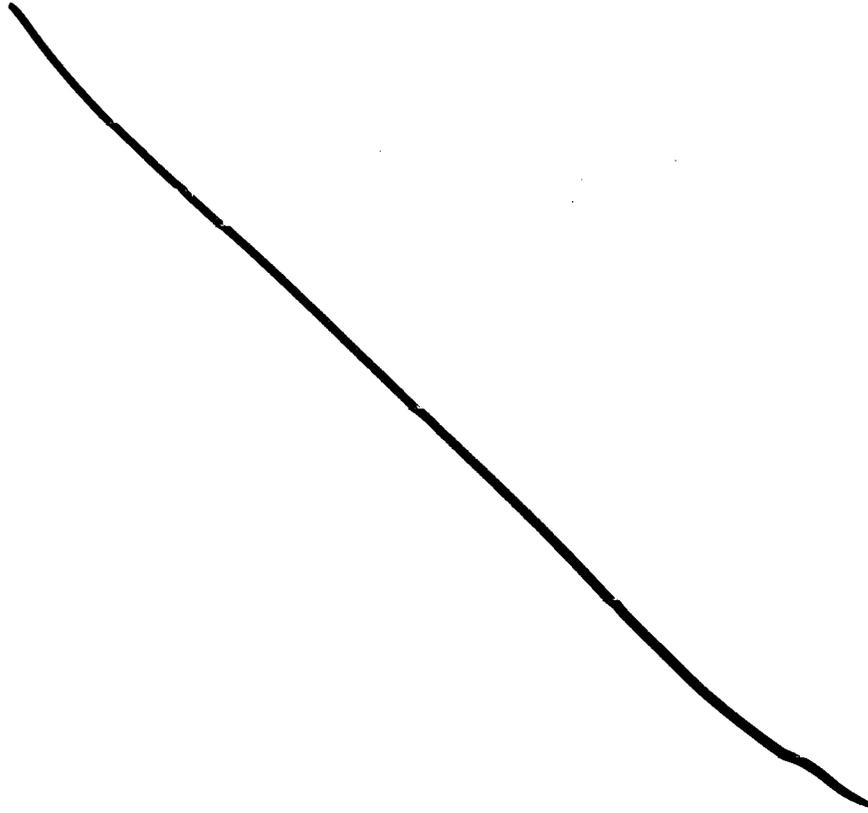
1. In the **DESCRIPTION** section, the sponsor proposed the following wording:



Discussion: This wording was reviewed by Dr. Chengyi Liang and the following alternative wording was suggested (and agreed upon by the sponsor):

SOLTAMOX™ solution, a nonsteroidal antiestrogen, is for oral administration. Each 5mL solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen and the following inactive ingredients: ethanol, glycerol, propylene glycol, sorbitol solution, licorice flavor, aniseed flavor, purified water.

2. In the **CLINICAL PHARMACOLOGY** section, **Absorption and Bioavailability** subsection, the sponsor proposed the following wording:



Discussion: This wording was reviewed by Dr. Roshni Ramchandani and the following alternative wording was suggested (and accepted by the sponsor):

A pharmacokinetic study was performed in healthy perimenopausal and postmenopausal female subjects to evaluate the bioavailability of Soltamox™(n=30) in comparison with the commercially available tamoxifen citrate tablets (n=33) under fasting conditions. A third arm evaluated the effect of food on Soltamox (n=16 evaluable). The rate and extent of absorption of Soltamox™ was found to be bioequivalent to that of tamoxifen citrate tablets under fasting conditions.

In the food effect arm, the C_{max} and AUC were comparable to the fasting group. T_{max} was slightly longer in the fed group. There was no difference in bioavailability of Soltamox™

Oral Solution between fed and fasting states, and therefore Soltamox™ can be given without regard to meals.

3. In the **CLINICAL PHARMACOLOGY** section, **Pediatric Patients** subsection, the sponsor proposed the following wording:

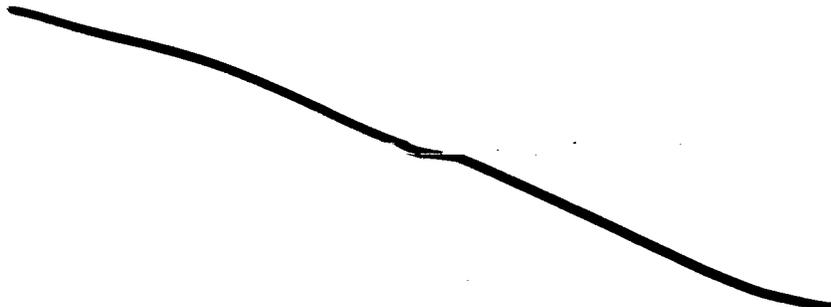
~~_____~~

The use of Soltamox in pediatric patients has not been evaluated.

4. In the **CLINICAL STUDIES** section, _____ subsection, the sponsor proposed the following wording:

~~_____~~

5. In the **PRECAUTIONS** section, **Nursing Mothers** subsection, the sponsor proposed the following wording:



Nursing Mothers

Tamoxifen has been reported to inhibit lactation. Two placebo-controlled studies in over 150 women have shown that tamoxifen significantly inhibits early postpartum milk production. In both studies tamoxifen was administered within 24 hours of delivery for between 5 and 18 days. The effect of tamoxifen on established milk production is not known.

There are no data that address whether tamoxifen is excreted into human milk. If excreted, there are no data regarding the effects of tamoxifen in breast milk on the breastfed infant or breastfed animals. However, direct neonatal exposure of tamoxifen to mice and rats (not via breast milk) produced 1) reproductive tract lesions in female rodents (similar to those seen in humans after intrauterine exposure to diethylstilbestrol) and 2) functional defects of the reproductive tract in male rodents such as testicular atrophy and arrest of spermatogenesis.

It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

6. In the **PRECAUTIONS** section, **Pediatric Use** subsection, the sponsor proposed the following wording:



The use of Soltamox in pediatric patients has not been evaluated.

7. In the **ADVERSE REACTIONS** section, the sponsor proposed the following wording as the second introductory paragraph:

Discussion: This wording was reviewed by Drs. Ramzi Dagher and Roshni Ramchandani and the following alternative wording was suggested (and agreed upon by the sponsor):

In one single-dose pharmacokinetic study in healthy perimenopausal and postmenopausal female volunteers, throat irritation was reported by 3 of 60 evaluable subjects (5.0%) in the Soltamox™ treatment groups while none of the subjects in the tamoxifen reference group reported this event. All events were mild and occurred within an hour after dosing. All events were resolved within 24 hours.

8. In the **ADVERSE REACTIONS** section, subsection, the sponsor proposed the following wording:

9. In the **DOSAGE AND ADMINISTRATION** section, the sponsor proposed the following wording:

[Redacted]

Discussion: This wording was reviewed by the team and the following alternative wording was suggested (and agreed upon by the sponsor):

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening). A 20 mg dose of Soltamox™ is administered as 10 mL (equivalent to 2 teaspoons) of the oral solution.

10. In the **HOW SUPPLIED** section, the sponsor proposed the following wording:

[Redacted]

Discussion: This wording was reviewed by Dr. Chengyi Liang and the following alternative wording was suggested (and agreed upon by the sponsor):

SOLTAMOX™ Oral Solution is a sugar-free, clear colorless liquid, with licorice and aniseed odor and taste. It is supplied in a 150mL bottle, each 5mL solution contains 15.2 mg tamoxifen citrate, equivalent to 10 mg tamoxifen. NDC (# not available at this time).

Do not store above 25° C (77° F). Store in the original package in order to protect from light. Use within 3 months of opening. Storage: DO NOT freeze or refrigerate.

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Discussion: No changes were requested by the team.

15. Minor editorial changes have been made throughout the package insert and Medication Guide.

Discussion: Some of the minor differences between the Soltamox proposed labeling and Nolvadex approved labeling were typographical errors and the sponsor has corrected those. Other minor editorial changes, i.e., replacing the term Nolvadex with tamoxifen citrate throughout the labeling, are acceptable.

RECOMMENDATIONS:

The final labeling and Medication Guide incorporating the Division's recommended wording (as agreed upon by the sponsor) will be attached to the APPROVAL letter for NDA 21-807.

Christy Cottrell
Consumer Safety Officer

Concurrence: /dp/ 9-29-05
Dotti Pease
Chief, Project Management Staff

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this page is the manifestation of the electronic signature.**

/s/

Christy Cottrell
10/31/2005 02:39:27 PM
CSO

Dotti Pease
11/1/2005 12:56:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-807

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard, 14th floor
East Brunswick, NJ 08816

Attention: Briti Kundu
Senior Director, Regulatory Affairs

Dear Ms. Kundu:

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: Soltamox Oral Solution (tamoxifen citrate)

Date of Application: December 23, 2004

Date of Receipt: December 27, 2004

Our Reference Number: NDA 21-807

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
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/

Dotti Pease
1/4/05 10:52:24 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-807 Supplement # Efficacy Supplement Type SE-

Trade Name: SOLTAMOX Oral Solution
Established Name: tamoxifen citrate
Strengths: 10mg/5mL

Applicant: Savient Pharmaceuticals, Inc.
Agent for Applicant: N/A

Date of Application: December 23, 2004
Date of Receipt: December 27, 2004
Date clock started after UN: January 12, 2005
Date of Filing Meeting: February 24, 2005
Filing Date: March 13, 2005
Action Goal Date (optional):

User Fee Goal Date: November 12, 2005

Indication(s) requested: Metastatic breast cancer; Adjuvant treatment of breast cancer; Ductal Carcinoma in Situ (DCIS); Reduction in breast cancer incidence in high risk women

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

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

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

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

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Nolvadex (NDA 17-970) still has the following exclusivities: M-20 expires 8-2-05 and PED-20 expires on 3-1-06.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

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

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

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? CRTs, package insert, carton and vial labels

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

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

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- 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 and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: Pre-IND #67,993

- End-of-Phase 2 Meeting(s) Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) November 7, 2003 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: February 24, 2005

BACKGROUND: This is a 505(b)(2) application providing for a new oral solution formulation of tamoxifen citrate. Nolvadex (tamoxifen citrate) Tablets is already approved under NDA 17-970. The Division met with Savient Pharmaceuticals in November 2003 for a Pre-IND/Pre-NDA meeting to discuss this application. Minutes can be found in DFS.

Note: The labeling for this application must include a Medication Guide and Gail risk model calculator as these are required elements for the Nolvadex approved labeling.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Dr. Richard Pazdur, Dr. Grant Williams, Dr. Ramzi Dagher, Dr. Nallaperumal Chidambaram, Dr. Ruth Wager, Dr. John Leighton, Dr. Yong-Cheng Wang, Dr. Rajeshwari Sridhara, Dr. Brian Booth, Dr. Roshni Ramchandani, Christy Cottrell

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

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Ramzi Dagher
Secondary Medical:	N/A
Statistical:	N/A (no stat review needed)
Pharmacology:	N/A (no P/T review needed)
Statistical Pharmacology:	N/A
Chemistry:	Ruth Wager
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Roshni Ramchandani
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	David Gan
Regulatory Project Management:	Christy Cottrell
Other Consults:	Joseph Grillo, DSRCS, DMETS

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

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

		N/A	<input checked="" type="checkbox"/>		YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
STATISTICS	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
BIOPHARMACEUTICS			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Biopharm. inspection needed?								
PHARMACOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
• GLP inspection needed?								
CHEMISTRY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>		
					YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
• Establishment(s) ready for inspection?					YES	<input type="checkbox"/>	NO	<input checked="" type="checkbox"/>
• Microbiology								

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

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

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Christy Cottrell
Regulatory Project Manager, HFD-150

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Appendix A to NDA Regulatory Filing Review

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) 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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Nolvadex (tamoxifen citrate) Tablets; NDA 17-970

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. 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"). This application provides for a change in dosage form, from tablets to oral solution.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. 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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
9. 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 (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 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. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(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): The patent on the listed drug is 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 as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that 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?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Christy Cottrell
5/10/05 02:20:05 PM
CSO
Answer to #13 is N/A.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST		
NDA 21-807	Efficacy Supplement Type SE-	Supplement Number
Drug: Soltamox (tamoxifen citrate) Oral Solution		Applicant: Savient Pharmaceuticals
RPM: Christy Cottrell		HFD-150 Phone # (301) 796-1347
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(X) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 17-970 for Nolvadex (tamoxifen citrate) Tablets</p>
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		(X) Standard () Priority
		3
		N/A
❖ User Fee Goal Dates		
		November 12, 2005
❖ 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 () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 		(X) Paid UF ID number 4915
<ul style="list-style-type: none"> • User Fee waiver 		() Small business () Public health () Barrier-to-Innovation () Other (specify) N/A
<ul style="list-style-type: none"> • User Fee exception 		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify) N/A
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		() Yes (X) No

<ul style="list-style-type: none"> This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> OC clearance for approval 	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> [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). 	21 CFR 314.50(i)(1) (X) (ii) () (iii)
<ul style="list-style-type: none"> [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). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><i>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 box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	(X) N/A (no paragraph IV certification) () Verified
<p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>() Yes () No</p>	() Yes () No
<p>(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)?</p> <p>() Yes () No</p>	() Yes () No
<p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

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

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

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 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.) 	Included- Yes, there is exclusivity remaining, but per OCC, it does not bar the 505(b)(2) approval
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" 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. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Tradename review: 6-29-05 NDA Regulatory Filing review: 5-10-05

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () 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)	N/A
• Most recent applicant-proposed labeling	Included
• Original applicant-proposed labeling	Included
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	CSO: 11-1-05 DDMAC: 6-30-05 DSRCS: No review needed (email)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	Included
• Reviews	N/A
❖ 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)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	November 7, 2003
• 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 reports (if applicable)	N/A

Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Included: 10-29-05
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	See PK review
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	Included: 9-29-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	Included: 6-21-05
CMC Information	
❖ CMC review(s) (indicate date for each review)	Included: 9-12-05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	9-12-05
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) 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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Christy Cottrell
11/3/2005 11:55:04 AM