CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-351

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Patent Information for 505(b)(1) Application

The undersigned declares that the patents listed below cover the formulation, composition, and/or method of use of Oxybutynin Transdermal System. This product is the subject of this application for which approval is being sought: NDA 21-351.

Number (Exp. Date)	Title	Type	Patent Owner
5,601,839 (04/26/2015)	Triacetin as a Penetration Enhancer for Transdermal Delivery of a Basic Drug	Drug Product	Watson Laboratories, Inc.
5,834,010 (04/26/2015)	Triacetin as a Penetration Enhancer for Transdermal Delivery of a Basic Drug	Drug Product	Watson Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

Dorothy A. Frank Date 20 August 2002

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Regulatory Liaison
US Proprietary Products
Regulatory Affairs Department

APPEARS THIS WAY
ON ORIGINAL

Patent Information for 505(b)(1) Application

The undersigned declares that the patents listed below cover the formulation, composition, and/or method of use of Oxybutynin Transdermal System. This product is the subject of this application for which approval is being sought: NDA 21-351.

Number (Exp. Date)	Title	Type	Patent Owner
5,164,190 (12/11/2010)	Subsaturated Transdermal Drug Delivery Device Exhibiting Enhanced Drug Flux	Drug Product	Watson Laboratories, Inc.
5,601,839 (04/26/2015)	Triacetin as a Penetration Enhancer for Transdermal Delivery of a Basic Drug	Drug Product	Watson Laboratories, Inc.
5,834,010 (04/26/2015)	Triacetin as a Penetration Enhancer for Transdermal Delivery of a Basic Drug	Drug Product	Watson Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

Dorothy A. Frank Date 04/24/01

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-351 SUPPL #

Trade Name Oxytrol Generic Name oxybutynin transdermal system
Applicant Name Watson Labortories, Inc. HFD- 580
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/__X_/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /__X_/

If yes, what type(SE1, SE2, etc.)?

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 /_X__/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

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

___three

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

YES /_X__/ NO /__ /

For oxybutynin chloride, Ditropan XL, NDA 20897

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

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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 /_X__/ NO /___/

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

NDA # 20-897 Ditropan XL

NDA # 18-211 Ditropan Syrup

NDA # 17-511 Ditropan Tablets

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 /_X__/

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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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X__/ 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 9:**

(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 /_X__/

(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 /_X__/

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 /_X__/

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:

Investigation #1, Study # 000011 (Phase 3)

Investigation #2, Study # 099009 (reanalysis, Phase 3)

Investigation #3, Study # _____

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 /__X_/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	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:

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NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #1, Study # 000011 (Phase 3)

Investigation #2, Study # 099009 (reanalysis, Phase 3)

Investigation #_3_, Study # _____

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

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

Investigation #1

IND # 50,489 YES /_X_/ NO /___/ Explain:

Investigation #2

IND # 50,489 YES /_X__/ NO /___/ Explain:

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

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(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 /_X__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Jean R. King
2/24/03 04:09:15 PM
CSO

Daniel A. Shames
2/25/03 06:43:03 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Debarment Certification

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

Dorothy A. Frank Date 20 August 2002

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Regulatory Liaison
US Proprietary Products
Regulatory Affairs Department

APPEARS THIS WAY
ON ORIGINAL

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

Dorothy A. Frank Date 04/24/01

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-351 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: August 30, 2003 Action Date: February 28, 2003

HFD 580 Trade and generic names/dosage form: Oxytrol™ (oxybutynin transdermal system) 3.9mg/day

Applicant: Watson Laboratories, Inc. Therapeutic Class: S3

Indication(s) previously approved: N/A

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

Number of indications for this application(s): 1

Indication #1: treatment of overactive bladder

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

❑ Yes: Please proceed to Section A.

❑ No: Please check all that apply: X 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. < 6 years old 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
X Other: Partial waiver granted in letter sent 10/23/01 as part of first nda submission cycle; hard copy of letter placed in February 2003 Action Packet with this document as reference material.

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.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Jean R. King
2/24/03 04:31:32 PM
CSO

final pediatric page for nda 21351 action packet

Daniel A. Shames
2/25/03 06:45:46 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

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

Applicant: NDA 21-351

Date of Application: August 29, 2002
Date of Receipt: August 39, 2002
Date of Filing Meeting:
Filing Date:

Indication(s) requested: treatment of overactive bladder

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

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

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

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ____X____ Waived (e.g., small business, public health) ___N/A_____
Exempt (orphan, government) ___N/A_____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID# 4085
Clinical data? YES __X__ NO _____ Referenced to NDA# ___N/A_____
Date clock started after UN _____N/A_____

User Fee Goal date: ____February 28, 2003____

Action Goal Date (optional) __N/A _____

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

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

- If electronic NDA, does it follow the Guidance? YES NO N/A
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO N/A

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, ___3___years NO

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

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

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:

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

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

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

List referenced IND numbers: 50,489

End-of-Phase 2 Meeting? Date 11/10/1999 NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 12/9/00 NO
If yes, distribute minutes before filing meeting.

Project Management

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

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES NO

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

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

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

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

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO N/A

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

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

If 505(b)(2), complete the following: N/A

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

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

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

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

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

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

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

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

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

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

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

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

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

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

Did the applicant:

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

  YES NO

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

  YES NO

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

  YES NO

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

YES NO

ATTACHMENT

MEMO OF FILING MEETING (DATED 10/21/02)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: October 21, 2002 **Time** 11:00 AM – 12:00 PM **Location**: PKLN; 17B-43

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system)

Indication: Overactive bladder

Sponsor: Watson Laboratories

Type of Meeting: Filing Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jean King, M.S., R.D.

FDA/CDER/DRUDP Attendees:
Mark Hirsch, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
DJ Chatterjee, Ph.D., Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sue Jane Wang, Ph.D., Statistician Team Leader, Division of Biometrics II (DBII0) @ DRUDP (HFD-580)
Ashok Batra, Medical Officer, DRUDP (HFD 580)
George Lyght, Project Manager, DRUDP (HFD 580)
Jennifer Mercier, Regulatory Health Project Manager, DRUDP (HFD 580)
Rajiv Agarwal, Chemist, Division of New drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Meeting Objective: To discuss the fileability of this resubmission to the sponsor's Not Approvable letter dated March 26, 2002.

Issues Discussed/Decisions Made:

Clinical:

- This application is fileable; all deficiencies in the Not Approvable letter have been addressed in this resubmission.
- The sponsor has withdrawn [redacted] from the application.
- The sponsor did not demonstrate a significant reduction in urinary frequency in study O99009, a secondary endpoint that FDA described as "clinically important" in establishing efficacy for treatment of OAB. Re-analysis of this same trial still does not support statistical significance for micturation frequency.
- The sponsor provided a reanalysis of the data in O009009 study to account for certain diary transcription errors.
- The sponsor provided additional data on skin irritation of Oxytrol 3.9 mg/day.
- The sponsor provided an entirely new phase 3 report: O00011.

Statistics:

- This application is fileable.
- The sponsor has submitted a new Integrated Summary of Efficacy (ISE) for this resubmission.
- From a cursory review of the data, it seems that the sponsor still did not demonstrate significant reduction in urinary frequency in study O99009.
- Electronic datasets for new study (O00011) and re-analysis of old study (O99009) were submitted and are acceptable for review.

Clinical Pharmacology and Biopharmaceutics:

- This application is fileable.
- The sponsor submitted an additional PK/PD study for safety only.
- A brief review is expected.

Chemistry:

- This application is fileable.
- The only chemistry issues are package insert, carton and container labeling; the sponsor has submitted the carton label for review. Carton and container labels have already been sent to DMETS for consult.

Action Items:

- The PDUFA Goal Date is February 28, 2003; the action package should be to the Division Director by February 21, 2003; to the Medical Officer Team Leader by February 7, 2003.
- Dr. Batra will be completing the Financial Disclosure review.
- Dr. Batra will pick clinical sites for inspection by DSI. PM will then send a consult to DSI.

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/s/

Jean R. King
2/24/03 04:02:03 PM
CSO

Jean R. King
2/24/03 04:06:05 PM
CSO

Teleconference Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 3.9 mg/day)

Date: February 21, 2003 **Time** 10:45 AM – 11:00 AM

FDA/CDER/DRUDP Attendees:
Mark Hirsch, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
Jean King, Project Manager DRUDP (HFD-580).

Watson Laboratories, Inc. Attendees:
David Campbell, Manager, Regulatory Affairs
Greg Torre, Vice President of Regulatory Affairs

Background: FDA phoned Watson to discuss Watson's comments to the Division's annotated PPI faxed to Watson Laboratories on February 19, 2003.

Issues discussed/Decisions Made:

1. Mr. Campbell and Mr. Torre presented the following edits to the Patient Package Insert (PPI) for discussion and concurrence from Dr. Hirsch on behalf of the Division:

   - Issue 1: On Page 1, paragraph 1 under "Oxytrol" section, change from:

   Change To: Read this information carefully you begin treatment. Read the information whenever you get more medicine; there may be something new.

   Response: Dr. Hirsch concurred with the proposed edit; a final review of Watson's annotated PPI will be made upon receipt of expected faxed submission (Watson will submit a hard copy to the NDA for archival purposes).

   - Issue 2: On Page 1, paragraph 2 under "What is Oxytrol" section, correct typographical error of "onself" to "oneself".

   Response: Dr. Hirsch concurred.

   - Issue 3: On Page 1, paragraph 3 under "What is Oxytrol" section, change from ——— to "tablets" in the last sentence.

   Response: Dr. Hirsch concurred.

- Issue 4: On Page 3, Under "What should I avoid while using Oxytrol" section, Watson suggests deleting the following sentence as it is reiterated in similar language under "What are the possible side effects of Oxytrol" section on page 4. Delete:

Response: Dr. Hirsch concurred.

- Issue 5: On Page 3, Under " section, Watson suggests modifying the following sentence to reduce unnecessary calls to physician:

Change to: If irritation continues, tell your doctor.

Response: Dr. Hirsch concurred.

- Issue 6: On Page 5, Paragraph 2 under "How should I use Oxytrol" section, change from:

Change to: You may wish to try different locations when using OXYTROL to find the locations that are most comfortable for you and where clothing will not rub against it.

Response: Dr. Hirsch concurred.

- Issue 7: On Page 6, paragraph 1 under first set of illustrations, change from:

Each patch is sealed in its own protective pouch. When you are ready to put on the OXYTROL patch, pouch and remove the patch. Apply the patch to your skin right away. Do not keep or store the outside the sealed pouch.
Change to: Each patch is sealed in its own protective pouch. When you are ready to put on the OXYTROL patch, tear open the pouch and remove the patch. Apply the patch to your skin right away. Do not keep or store the patch outside the sealed pouch.

Response: Dr. Hirsch concurred.

-

Change to: Touching the adhesive may cause the patch to fall off early.

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/s/

Jean R. King
2/24/03 03:31:40 PM
CSO

Mark S. Hirsch
2/24/03 04:21:50 PM
MEDICAL OFFICER
I concur.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Watson Laboratories-Utah

417 Wakara Way, Salt Lake City UT 84108 / Phone (801) 588-6200 / FAX (801) 588-6232

FAX

PAGE 1 OF 6

TO:	Jean King
	FDA / CDER / DRUDP
FAX:	(301) 827-4267
FROM:	John W. Smith Direct phone: 801 588 6377 e-mail: john.smith@watsonpharm.com
DATE:	2003-02-21
Subject:	NDA 21-351 (Oxytrol)

Ms. King:

Following this cover page, you will find our final patient information insert for Oxytrol. We will also send a hard copy of this submission to the NDA.

Best regards,

John W. Smith
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

21 February, 2003

Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
(HFD-580)
Center for Drug Evaluation and Research
Document Room 17B-20
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Application

RE: NDA #21-351: OXYTROL™ oxybutynin transdermal system 3.9 mg/day.
Amendment to a Pending Application: Final Draft Patient information Insert

Dr. Shames:

Watson is hereby submitting the final draft patient information insert. The content of this insert was discussed and agreed upon with Dr. Mark Hirsch representing DRUDP in a teleconference on February 21, 2003.

If you have any questions about the information provided, please contact me by phone at 973-355-8159 or by fax at 973-355-8582.

Sincerely,

David L. Campbell, R.A.C.
Manager, Regulatory Liaison
U.S. Proprietary Products

APPEARS THIS WAY ON ORIGINAL

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

5 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Teleconference Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 3.9 mg/day)

Date: February 14, 2003 **Time** 1:05 PM – 1:20 PM

FDA/CDER/DRUDP Attendees:
Mark Hirsch, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
Jean King, Project Manager DRUDP (HFD-580).

Watson Laboratories, Inc. Attendees:
David Campbell - Manager, Regulatory Affairs

Background: FDA phoned Watson Laboratories. The teleconference was initiated at the request of Dr. Hirsch to discuss receipt of Watson's revised PI faxed to the Division on February 13, 2003.

Issues discussed/Decisions Made:

1. Dr. Hirsch conveyed the following additional Division comments to Mr. Campbell regarding Watson's revised Package Insert (PI) dated 2/13/03:

   - Issue 1: In Figure 2 on page 3 and Figure 4 on page 5 of the PI, clarify in the title of each figure the abbreviation "Cp" used on the Y-axis as follows:

     Figure 2: Average plasma oxybutynin concentrations (Cp) in 24 healthy male and female volunteers during single-dose application of **OXYTROL** 3.9 mg/day to the abdomen, buttock, and hip (System removal at 96 hours).

     Figure 4: Average plasma concentrations (Cp) measured after a single, 96-hour application of the **OXYTROL** 3.9 mg/day system (AUC_{inf}/96) and a single, 5 mg. oral immediate-release dose of oxybutynin chloride (AUC_{inf}/8) in 16 healthy male and female volunteers.

     Response: Mr. Campbell concurred with proposed edit on behalf of Watson Laboratories.

   - Issue 2: In Table 4 on page 8 of the PI, add "(Study 2)" to title to clarify referenced protocol as follows:

     Table 4: Mean and median change from baseline to end of treatment (Week 12 or last observation carried forward) in incontinence episodes, urinary frequency, and urinary void volume in patients treated with **OXYTROL** 3.9 mg/day or placebo for 12 weeks (Study 2).

     Response: Mr. Campbell concurred with proposed edit on behalf of Watson Laboratories.

   - Issue 3: Under the Clinical Pharmacology section on page 2 of the PI, revise the third sentence as follows:

     Change From:

Change To: "In patients with conditions characterized by involuntary by detrusor contractors, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction."

Response: Mr. Campbell concurred with proposed edit on behalf of Watson Laboratories.

- Issue 4: Under the Special Populations section on page 6 of the PI, delete the [redacted] in the Geriatric statement as follows:

Special Populations
Geriatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were similar in all patients studied [redacted]

Response: Mr. Campbell concurred with proposed edit on behalf of Watson Laboratories. Additionally, Mr. Campbell agreed to send via fax to the Division (and hard copy submission to NDA) their revised PI with a cover letter stating that the PI constitutes their final PI based on discussions held with the Division.

2. Dr. Hirsch informed Mr. Campbell that the Division would proceed with its ongoing review of the Patient Package Insert (PPI).

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/s

Jean R. King
2/19/03 03:41:22 PM
CSO

Mark S. Hirsch
2/21/03 01:55:27 PM
MEDICAL OFFICER
I concur.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 3.9 mg/day)

Date: February 13, 2003 **Time** 12:00 PM – 12:15 PM

FDA/CDER/DRUDP Attendees:
Mark Hirsch, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)
Ashok Batra, Medical Officer, DRUDP (HFD 580)
Jean King, Project Manager DRUDP (HFD-580).

Watson Laboratories, Inc. Attendees:
David Campbell - Manager, Regulatory Affairs

Background: FDA phoned Watson Laboratories. The teleconference was initiated at the request of Mr. Campbell.

Issues discussed/Decisions Made:

1. Mr. Campbell confirmed receipt of the Division's comments on Watson Labrotories' proposed Package Insert (PI) for Oxytrol. Mr. Campbell requested clarification of the Division's edits to their original Table 5 on page 14 of the Division's February 12, 2003 fax, which now presents the information in two separate tables (Tables 5 and 6).

   - Question 1: In the new Table 6, the Placebo N equals — Watson Laboratories reviewed their data and confirmed that the N should remain 117. Please clarify.

     Response: Yes. The Placebo N should remain 117; ————————————

   - Question 2: Why does the Division propose to separate the information provided in Watson's proposed —

   - Question 3: In Watson's proposed Table 5, ———————— was listed. However, in the Division's proposed Table 6, ———————— was omitted. Please clarify.

APPEARS THIS WAY
ON ORIGINAL

- Question 4: Watson had provided revised text for the "Adhesion" section of the label in response to faxed comments from the Clinical Pharmacology and Biopharmacuetics reviewer (sent on 2/05/03). The revised text does not appear in the Division's proposed label changes. Please clarify.

  Response: The label sent to Watson contain the DRUDP-preferred Adhesion Text. Watson may submit any proposed text changes to the Adhesion section in response to yesterday's faxed complete Division edits.

- Question 5: Mr. Campbell asked clarification on expected further label reviews.

  Response: The Division will review Watson's complete response to the PI, which should include an updated annotated PI. Any annotations should be included in a cover letter to facilitate the Division's review. Once a final PI is mutually agreed upon, the Division will complete its ongoing review of the patient package insert (PPI) and will forward compiled review comments.

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/s/

Jean R. King
2/19/03 03:40:10 PM
CSO

Mark S. Hirsch
2/20/03 01:52:23 PM
MEDICAL OFFICER
I concur.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

INFORMATION REQUEST LETTER

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, UT 84108-1255

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Campbell:

Please refer to your August 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytrol (oxybutynin) transdermal system, 3.9 mg day.

We are reviewing the Patient Package Information (PPI) section of your August 29, 2002 submission and have the following attached labeling edits. We request a prompt written response to the attached labeling edits in order to continue our evaluation of your NDA.

If you have any questions, call Jean King, M.S., R.D., Regulatory Project Manager, at 301- 827- 4260.

Sincerely,

{See appended electronic signature page}

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

Cc: Enclosure

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6 Page(s) Withheld

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/s/

Daniel A. Shames
2/19/03 04:48:16 PM

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/s/

Daniel A. Shames
2/19/03 04:58:47 PM

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ON ORIGINAL

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

APPEARS THIS WAY
ON ORIGINAL

14 February, 2003

Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
(HFD-580)
Center for Drug Evaluation and Research
Document Room 17B-20
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Amendment to a Pending Application

RE: **NDA #21-351**: OXYTROL™ oxybutynin transdermal system 3.9 mg/day.
Amendment to a Pending Application: Final Draft Package Insert

Dr. Shames:

Watson is hereby submitting the final draft package insert. The content of this label was agreed upon between Watson personnel and Dr. Mark Hirsch representing DRUDP in a teleconference on February 14, 2003.

If you have any questions about the information provided, please contact me by phone at 973-355-8159 or by fax at 973-355-8582.

Sincerely,

for DLC

David L. Campbell, R.A.C.
Manager, Regulatory Liaison
U.S. Proprietary Products

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ON ORIGINAL

19 Page(s) Withheld

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✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Charles F. White, M.D.
Coastal Clinical Research, Inc.
100 Memorial Hospital Drive
Annex Building, Suite 3-B
Mobile, Alabama 36608

FEB 13 2003

Dear Dr. White:

Between January 13 and 15, 2003, Ms. Dana M. Daigle and Mr. Matthew B. Thomaston, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #O00011, entitled: "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Comparing Oxybutynin Transdermal Systems versus Tolterodine Long Acting Capsules in Patients with Overactive Bladder") of the investigational drug oxybutynin chloride, performed for Watson Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that, except for minor recordkeeping deficiencies that were discussed with you during the inspection, you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigators Daigle and Thomaston during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice I, by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3001237223

Field Classification: NAI
Headquarters Classification:
_____ 1)NAI
_X___2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

No Form FDA 483 was issued and minor deficiencies were discussed with the principal investigator.

cc:
HFA-224
HFD-580 Doc.Rm. NDA #21-351
HFD-580 Division Director
HFD-580 MO Batra
HFD-580 PM Mercier
HFD-46/c/r/s/ GCP File #10804
HFD-46 Blay
HFD-47 Hajarian
HFR-SE450 Herd
HFR-SE450 BIMO Monitor Michael Roosevelt
HFR-SE4550 Field Investigator Daigle
HFR-SE3565 Field Investigator Thomaston
GCF-1 Seth Ray
F/t: sg:2/12/03
r/d:GRH:2/10/03

O:\GRH\WHITE NAI.DOC

Reviewer's Note to Review Division's Medical Officer

Twenty-nine subjects were screened. Twenty-three subjects were randomized. Five subjects were terminated. Two subjects withdrew consent, one subject was terminated due to exclusionary medication and post-void residual volume >150 mL, one subject was lost to follow up and one subject due to worsening back pain. The records of 8 subjects were reviewed in detail.

No significant deficiencies were noted. Several minor deficiencies were discussed with the prinicipal investigator. Although the protocol excluded subjects with a post-void volume of ≥ 150 mL, subject 4506 was enrolled and dispensed the study drug. One source document (ECG strip) was missing; several subjects did not sign the current version of the informed consent; and the handwriting of one subject's diaries was inconsistent, implying that someone other than the subject filled out the diary.

In summary, no significant deficiencies were noted and no Form FDA 483 was issued. The data from subjects at this site can be used for evaluation of Protocol O00011 submitted in support of NDA 21-351for review by FDA.

Watson Laboratories-Utah

417 Wakara Way, Salt Lake City UT 84108 / Phone (801) 588-6200 / FAX (801) 588-6232

FAX

PAGE 1 OF 15

TO:	Jean King, Regulatory Project Manager
	FDA / CDER / DRUDP
FAX:	(301) 827-4267
FROM:	John W. Smith Direct phone: 801 588 6377 e-mail: john.smith@watsonpharm.com
DATE:	2003-02-13
Subject:	NDA 21-351: Oxytrol

Ms. King:

Following this cover page, please find Watson's response to your fax of February 12. We will send a hard copy of this response to the NDA.

Best regards,

John W. Smith
Associate Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

FDA proposed Table 6 from the Adverse Reactions Section on page 14 of February 12, 2003 fax:

Adverse Event*	Placebo (N= —)		OXYTROL (3.9 mg/day) (N=121)	
	N	%	N	%
Application site pruritis	5	4.3%	17	14.0%
Application site erythema	2	1.7%	10	8.3%
Dry mouth	2	1.7%	5	4.1%
Constipation	0	0.0%	4	3.3%
Application site rash	1	0.9%	4	3.3%
Application site macules	0	0.0%	3	2.5%
Abnormal vision	0	0.0%	3	2.5%

Watson proposed Table 6 with editorial changes:

Adverse Event*	Placebo (N= ~~—~~ 117)		OXYTROL (3.9 mg/day) (N=121)	
	N	%	N	%
Application site pruritis	5	4.3%	17	14.0%
Application site erythema	2	1.7%	10	8.3%
Dry mouth	2	1.7%	5	4.1%
Constipation	0	0.0%	4	3.3%
Application site rash	1	0.9%	4	3.3%
Application site macules	0	0.0%	3	2.5%
Abnormal vision	0	0.0%	3	2.5%

In all other cases, we have accepted your changes. A revised package insert is included, with deleted text indicated by ~~strikeout~~ and added text indicated by double underline.

If you have any questions about the information provided, please contact me by phone at 973-355-8159 or by fax at 973-355-8582.

Sincerely,

For DLC

David L. Campbell, R.A.C.
Manager, Regulatory Liaison
U.S. Proprietary Products

APPEARS THIS WAY
ON ORIGINAL

12 Page(s) Withheld

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✓ § 552(b)(5) Draft Labeling

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 12, 2003

To: David Campbell

Company: Watson Laboratories

Fax number: 973-355-8582

Phone number: 973-355-8159

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-351 Label Comments

Total no. of pages including cover:

Comments: Please find attached an IR letter pertaining to our ongoing label review for NDA 21.351.

Document to be mailed: X YES NO

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

INFORMATION REQUEST LETTER

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, UT 84108-1255

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Campbell:

Please refer to your August 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytrol (oxybutynin) transdermal system, 3.9 mg/day.

We are reviewing the Labeling section of your August 29, 2002 submission and have the following attached labeling edits. We request a prompt written response to the attached labeling edits in order to continue our evaluation of your NDA.

If you have any questions, call Jean King, M.S., R.D., Regulatory Project Manager, at 301- 827- 4260.

Sincerely.

{See appended electronic signature page}

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

Cc: Enclosure

APPEARS THIS WAY
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31 Page(s) Withheld

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/s/

Daniel A. Shames
2/26/03 06:03:19 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2003

To: David Campbell

From: Jean King

Company: Watson Laboratories

Division of Division of Reproductive and Urologic Drug Products

Fax number: 801-583-6042

Fax number: 301-827-4267

Phone number: 801-558-6200

Phone number: 301-827-4260

Subject: NDA 21-351 Label Review Initial Comments

Total no. of pages including cover: 3

Comments: Per your request, please find attached a copy of the January 30, 2003 IR letter pertaining to our ongoing label review for NDA 21,351.

Document to be mailed: YES NO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

INFORMATION REQUEST LETTER

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, UT 84108-1255

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Campbell:

Please refer to your August 29, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug. and Cosmetic Act for Oxytrol (oxybutynin) transdermal system, 3.9 mg/day.

We also refer to your submission dated December 19, 2002 in response to our request for color mockups of the primary and secondary packaging materials. We are reviewing the Chemistry, Manufacturing and Controls, as well as the Division of Medication Errors and Technical Support sections of your submission and have the following comments and information requests.

1.) The — ; is distracting and obscures the —
in the proprietary name. Delete the —

2.) Delete the —

Please include these changes in your submission of anticipated final color mockups of the primary and secondary packaging materials. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Jean King, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Jean R. King
2/5/03 03:03:44 PM
CSO

Jean R. King
2/5/03 03:06:01 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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/s/

Moo-Jhong Rhee
1/30/03 01:42:42 PM

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2003

To: David Campbell

Company: Watson Laboratories

Fax number: 801-583-6042

Phone number: 8801-558-6200

From: Jean King

Division of Division of Reproductive and Urologic Drug Products

Fax number: 301-827-4267

Phone number: 301-827-4260

Subject: NDA 21-351 Label Review Initial Comments

Total no. of pages including cover: 2

Comments: Please find below an information request from our ongoing label review for NDA 21,351. An immediate response is requested.

Document to be mailed: YES NO

APPEARS THIS WAY ON ORIGINAL

The Division's recommendation pertains to the following section written in your proposed package insert:

Watson Laboratories current proposed text:

The Clinical Pharmacology and Biopharmaceutics reviewer requests that you complete the following recommended revised text by replacing the blanks (represented by # symbols) with the correct information (i.e., the numbers and provide the source of the numbers, annotation, etc.).

Division's Recommended Text Changes:

Adhesion
Adhesion was periodically evaluated during the Phase III studies. Of the OXYTROL applications in the Phase III trials, were observed at clinic visits to have became completely detached and became partially detached during routine clinic use. Similar to the pharmacokinetic studies, > of the systems applied in the Phase III studies were assessed as being ≥75% attached and thus would be expected to perform as anticipated.

If you have any questions, please notify me immediately at 301-827-7270.

Jean King, M.S., R.D.
Regulatory Project Manager
FDA/CDER/
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane
Rockville, MD 20857

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/s/

Jean R. King
2/5/03 03:13:11 PM
CSO

Jean R. King
2/5/03 03:14:59 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

King, Jean

From: King, Jean
Sent: Thursday, January 30, 2003 11:58 AM
To: 'DCampbell@Watsonpharm-FDA.COM'
Subject: RE: Oxytrol - Color Mockups

HI David,
I can not find the patient insert (label) word document in my files of email correspondences. Would you take a minute to resend this to me today. Thank you. Jean

-----Original Message-----
From: DCampbell@Watsonpharm-FDA.COM [mailto:DCampbell@Watsonpharm-FDA.COM]
Sent: Thursday, December 19, 2002 2:36 PM
To: King, Jean
Subject: RE: Oxytrol - Color Mockups

Jean,

I've attached the requested files.

Best Regards,

David

APPEARS THIS WAY
ON ORIGINAL

"King, Jean" <KINGJE@CDER.FDA.GOV>

12/18/2002 12:04 PM

To: "'DCampbell@Watsonpharm-FDA.COM'" <DCampbell@Watsonpharm-FDA.CC
cc:
Subject: RE: Oxytrol - Color Mockups

HI David,
I left you a vm regarding the final mock-ups for Dr. Agarwal. While you get the requested two copies in the mail, can you send a pdf file of the carton so the DMETS reviewer can get started with it.
thanks again, jean
-----Original Message-----
From: DCampbell@Watsonpharm-FDA.COM [mailto:DCampbell@Watsonpharm-FDA.COM]
Sent: Wednesday, December 18, 2002 10:45 AM
To: kingje@cder.fda.gov
Subject: Oxytrol - Color Mockups

Jean,

As we discussed in the teleconference last week, we are in the process of changing the artwork for the Oxytrol packaging materials. This process is not quite as far along as I thought. We do have color mockups, but they contain some additional information that can't be removed at this stage. I've attached an example of the pouch mockup for you to take a look at. If this is acceptable, I can send the copies to you today. Otherwise, it will likely be next week.

Best Regards,

David

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King, Jean

From: King, Jean
Sent: Thursday, January 02, 2003 1:52 PM
To: 'DCampbell@Watsonpharm-FDA.COM'
Subject: RE: NDA 21-351 - Stat Reviewer's Request

Hi Davic,

I will check with Sue Jane on her availability and get back to you with time and date. On another topic that I need to ask for Dr.. Agawarl, do you have final or near final patient and physician package inserts available that you can send us (we received the four desk copies of color mock-ups for label-thank you again for sending those. Do you have a better sense of when the final mock-ups will be available?) thank you again.
Jean

-----Original Message-----
From: DCampbell@Watsonpharm-FDA.COM [mailto:DCampbell@Watsonpharm-FDA.COM]
Sent: Thursday, January 02, 2003 1:47 PM
To: kingje@cder.fda.gov
Subject: NDA 21-351 - Stat Reviewer's Request

Jean,

We're close to having the SAS programs that Dr. Wang requested. Our Statisticians would like to have a teleconference with her to discuss these programs and the discrepancies that she indicated she found. Would it be possible to set up a teleconference for this afternoon or tomorrow morning?

Thanks and Best Regards,

David

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Office of Drug Safety

Memo

To: Daniel Shames, MD
Director, Division of Reproductive & Urologic Drug Products
HFD-580

From: Kevin Dermanoski, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Jean King
Project Manager, Division of Reproductive & Urologic Drug Products
HFD-580

Date: January 2, 2003

Re: ODS Consult 00-0327-1; Oxytrol (Oxybutynin Transdermal System); NDA 21-351

This memorandum is in response to a September 12, 2002 request from your Division for a re-review of the proprietary name, Oxytrol. In our consult dated May 1, 2001(ODS Consult #00-0327), the Division of Medication Errors and Technical Support (DMETS) did not have any objections to the use of the proprietary name, Oxytrol. Since the initial review, DMETS identified three additional proprietary names with potential for sound-alike and/or look-alike similarities with Oxytrol. These products are Ogestrel, Oxycet, and Axocet. See Table-1 (page-2) for a side-by-side comparison of Oxytrol, Ogestrel, Oxycet, and Axocet. Although there are sound-alike and/or look-alike similarities with these products, the differences in dosage strength, route and frequency of administration, and formulation will minimize the potential for medication errors due to name confusion.

Table 1. Comparison of Oxytrol, Ogestrel, Oxycet and Axocet

Proprietary Name	Oxytrol	Ogestrel	Oxycet	Axocet*
Status	Pending NDA	Approved NDA	Approved NDA	ANDA
Established Name	Oxybutynin	Norgestrel/Ethinyl Estradiol	Acetamenophen/ Oxycodone	Acetaminophen/ Butalbital
Sponsor	Watson	Watson	Mallinckrodt	Savage (Distributor)
Indication	Urinary incontinence	Contraception	Pain	Pain
Dosage Strength	Delivers 3.9 mg/day	0.5 mg/0.5 mg	500 mg/5 mg	650 mg/50 mg
How Supplied	"Patient Calendar Box" (carton) containing either 8 or 24 systems (patches)	Unit-of Use package containing 21 or 28 tablets	No longer marketed using this proprietary name.	Bottles of 100 tablets.
Usual Dose and Range	1 patch applied and replaced twice weekly.	1 tablet	1-2 capsules	1-2 tablets
Frequency of Administration	Twice Weekly	Once Daily	Every 4-6 hours or as needed.	Every 4-6 hours or as needed.
Route of Administration	TOPICAL (abdomen, hip, or buttocks)	ORAL	ORAL	ORAL
Dosage formulation	TRANSDERMAL PATCH	TABLET	CAPSULE	TABLET
* Axocet is the proprietary name used by the Distributor Savage.				

During the initial review, labels and labeling were not submitted to DMETS for review. Pouch labeling, carton labeling, and insert labeling, were submitted to DMETS during this review; however, the container label and patient information leaflet were not submitted. DMETS has attempted to focus on safety issues relating to possible medication errors during the review of the container labels and carton labeling of Oxytrol. We have identified several areas of possible improvement.

A. GENERAL COMMENTS

1. The [redacted] is distracting and obscures the proprietary name. Delete the [redacted]
2. Relocate and decrease the prominence of the net quantity statement (i.e., Contains 24 transdermal system) to ensure there is sufficient space between the expression of the strength and the net quantity statement.
3. In the Information for Patients subsection, the wording: "A new application site should be selected with each new system....." should be revised to "[redacted] s." The original wording may lead patients to think that they must select a site other than the abdomen, hip, or buttock for application.
4. The pouch labeling should also contain the patient instruction statement noted in Comment #3 regarding the rotation of the site of patch application. Revise accordingly.

In summary, DMETS does not object to the use of the proprietary name, Oxytrol. However, we recommend implementation of the label and labeling revisions outlined above. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name along with the labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out objections based upon approvals of other proprietary and or established names from this date forward.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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/s/

Kevin Dermanoski
1/6/03 11:45:32 AM
PHARMACIST

Denise Toyer
1/8/03 02:18:26 PM
PHARMACIST

Carol Holquist
1/13/03 11:20:50 AM
PHARMACIST

APPEARS THIS WAY
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APPEARS THIS WAY
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Internal Meeting Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 2.6 mg and 3.9 mg/day)

Date: December 10, 2002 **Time** 11:00 AM – 12:00 PM

FDA/CDER/DRUDP Attendees:
Mark Hirsch, Medical Team Leader
Ashok Batra, Medical Officer
Jean King, Project Manager
Rajiv Agarwal, Chemist

Background: This was the 4-month internal team meeting to discuss status of ongoing reviews for this resubmitted NDA.

Issues discussed/Decisions Made:

1. Dr. Batra reported that his review was ongoing and progressing well. In summary, the most recent study submitted for this NDA (Protocol 000011) showed that the Oxytrol TDS decreased incontinence episodes three times daily as compared to twice daily in the placebo group. There was statistical significance demonstrated ($p = .01$) for urinary incontinence. The variable, urinary frequency, showed clinical significance, but not statistical significance ($p = 0.1$). However, in a post-hoc analysis of a subgroup of patients who had 14 or more episodes of micturia per day, statistical significant was demonstrated ($p= .0036$) for frequency reduction.

2. In the submitted reanalysis of study 0099009, his review indicates that there is statistical significance demonstrated for the efficacy of oxytrol TDS to decrease incontinence episodes as well ($p = .0265$). In terms of the variable, urinary frequency, this 009909 study demonstrated clinically significant difference between treatment and placebo groups; statistical significance is still under review.

3. Dr. Agarwal reported that the CMC review had been completed with the first NDA submission in March 2002. No additional information for CMC was included in this resubmission. A teleconference is scheduled for December 12, 2002 to verify that the CMC submission remains the same and to request most current mock-ups of pouch and carton label.

4. Outstanding items to be addressed:

a) Dr. Batra will complete the financial disclosure as part of his clinical review.

b) Dr. Batra will also determine the need for a DSI consult for select sites.

c) Jean will convey the following to the statistician, Sue Jane Wang: Has the requisite data requested following the 3-month status meeting been made to and received from the sponsor?

d) Jean will convey the following to the clinical pharmacologist, Young Choi: what is the status of your review and please provide an update on any issues from PK perspectives. Additionally, please keep the team apprised of any issues (i.e., adhesion data) possibly raised from your review of the wear study.

APPEARS THIS WAY ON ORIGINAL

e) **The schedule for the next internal team meetings are:**

Subject: Updated: NDA 21-351/Oxytrol/5 month status meeting
When: Tuesday, January 07, 2003 11:00 AM-12:00 PM .
Where: CDER PKLN 17B43 Conf Room -AR

Subject: Updated: NDA 21-351/Oxytrol/5.5 month status meeting
When: Tuesday, January 28, 2003 11:00 AM-12:00 PM.
Where: CDER PKLN 17B43 Conf Room -AR

f) **Internal Team goal dates also discussed at this meeting include**:

February 1, 2003: begin label discussions with Watson Labs

February 7, 2003: Action packet to Team Leader, Dr. Mark Hirsch

February 21, 2003: Action packet to Director, Dan Shames

February 28, 2003: PDUFA Action packet due date

g) Dr. Agarwal and Jean King informed team that they will hold a teleconference with Watson Laboratories to inquire whether there was any additional CMC data expected for this NDA submission and request hard copies of the final primary and secondary container label mock-ups (in color) to complete the CMC review. Additional copies will also be requested for DMETS.

h) Jean King will convey the following statistical request from Sue Jane Wang: please submit the computer program used to perform the RT-2 rank analysis (for the efficacy endpoint) for review.

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/s/

Jean R. King
12/23/02 09:14:13 AM

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M E M O R A N D U M

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

Date: December 20, 2001

From: Ashok Batra , M.D.
Medical Officer
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-351 (study 000011)

I have reviewed the financial disclosure information submitted by Watson Laboratories, Inc. in support of their NDA 21-351 for Oxytrol™ (oxybutynin transdermal system).

One pivotal Phase 3 study was conducted to assess the safety and efficacy of Oxytrol™ (oxybutynin transdermal system) for the treatment of patients with overactive bladder with symptoms of urge incontinence, urgency, and frequency. The financial disclosure information of that Study 099009 was reviewed by J. Best . The sponsor have now completed a confirmatory trial , the number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 000011 / Transdermal Oxybutynin in Patients with Urge Urinary Incontinence: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled StudyComparing Oxybutynin Transdermal Systems versus Tolterodine Long-Acting Capsules in Patients with Overactive Bladder.	Began after April 23,2001	Appropriate documentation received, no financial disclosure submitted

Documents Reviewed:

- Financial Certification Information (Form FDA 3454) submitted August 20 , 2001

Study 000011

Study 000011 started April 23,2001 and completed October 11, 2002 (open-label extension). There were 227 principal and subinvestigators (investigators) at 48 sites (320subjects) in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of Trial 000011 in NDA 21-351.

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/s/

Ashok Batra
12/22/02 05:22:09 PM
MEDICAL OFFICER

Mark S. Hirsch
12/27/02 04:18:24 PM
MEDICAL OFFICER
I concur.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Teleconference Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 3.9 mg/day)

Date: December 12, 2002 **Time** 1:00 PM – 1:15 PM

FDA/CDER/DRUDP Attendees:
Jean King, Project Manager
Rajiv Agarwal, Ph.D- Chemist Reviewer, DNDCII @ DRUDP (HFD-580).

Watson Laboratories, Inc. Attendees:
Steve Sanders - Vice President, Proprietary Research and Development
Dorothy Frank - Executive Director, Regulatory Affairs
Mamun Khan - Director, Analytical Services
Scott Gochnour - Executive Director, Transdermal Development
Mike Kimball - Manager, Transdermal Development
Jill Callahan - Manager, Technical Services
Steve Roberts - Director, Quality Compliance
David Campbell - Manager, Regulatory Affairs

Background: Jean King and Rajiv Agawarl phoned into Watson Laboratories' teleconference line. The teleconference was initiated at the request of Dr. Agawarl.

Issues discussed/Decisions Made:

1. Dr. Agarwal inquired whether there was any additional CMC data expected for this NDA submission.

   Response: Watson Laboratories reported that it was complete and no further CMC data would be submitted to this NDA packet.

2. Dr. Agarwal requested hard copies of the final primary and secondary container label mock-ups (in color) at this time to complete the CMC review. Jean King also conveyed a similar request from DMETS in order to complete their tradename consult. Jean King requested four copies of each so that two additional will be available to Division members if needed.

   Response: Watson Laboratories will submit the four copies for review; target date for submission is the week of December 16, 2002.

3. Jean King conveyed the following statistical request from Sue Jane Wang: please submit the computer program used to perform the RT-2 rank analysis (for the efficacy endpoint) for review.

   Response: Watson Laboratories will submit the computer program used to perform the RT-2 rank analysis (for the efficacy endpoint) for review; target date for submission is the week of December 16, 2002.

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/s/

Jean R. King
12/17/02 10:45:04 AM
CSO
additional signatures are not required

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Teleconference Minutes

NDA: 21,351 **Drug:** Oxytrol (oxybutynin transdermal system 3.9 mg/day)

Date: December 13, 2002 **Time** 1:00 PM – 1:15 PM

FDA/CDER/DRUDP Attendees:
Jean King, Project Manager DRUDP (HFD-580).
Sue-Jane Wang, Ph.D- Statistics Reviewer DRUDP (HFD-580).

Watson Laboratories, Inc. Attendees:
David Campbell - Manager, Regulatory Affairs

Background: Jean King and Sue-Jane Wang phoned Watson Laboratories. The teleconference was initiated at the request of Dr. Wang.

Issues discussed/Decisions Made:

1. Dr. Wang inquired whether an electronic submission of the computer program used to perform the RT-2 rank analysis (for the efficacy endpoint) could be sent for her ongoing review. Dr. Wang reiterated that the submission of this computer program was critical to receive expeditiously so that her review could proceed on time.

   Response: Watson Laboratories reported that the computer program was developed and completed by its CRO contractor and because they used a proprietary analysis software, Watson would have to complete requisite legal paperwork before the CRO would release the data sets. Watson Laboratories will submit the electronic data files as soon as possible; David Watson will keep Jean King apprised of any issues that may delay receipt. Target date for submission is the week of December 16, 2002.

3 Page(s) Withheld

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

___✓___ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., R.A.C.
Executive Director, Regulatory Liaison
417 Wakara Way
Salt Lake City, UT 84108

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Frank:

We acknowledge receipt on August 30, 2002 of your August 29, 2002 resubmission to your supplemental new drug application for OXYTROL™ (oxybutynin transdermal system 3.9 mg/day).

This resubmission contains additional clinical information, labeling information and safety update report submitted in response to our March 26, 2002 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the primary user fee goal date is February 28, 2003.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

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/s/

Margaret Kober
9/30/02 05:26:58 PM
Chief, Project Management Staff

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Meeting Minutes

Date: May 17, 2002 **Time:** 3:00-4:30 PM **Location:** PKLN; Conference Room "C"

NDA 21-351 **Drug:** Oxytrol™ (oxybutynin transdermal system)

Indication: overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Post-Action Meeting

Meeting Chair: Mark Hirsch, M.D.

External Lead: Greg Torre

Meeting Recorder: Jennifer Mercier

APPEARS THIS WAY ON ORIGINAL

FDA Attendees:
Mark Hirsch, M.D. - Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCBP @ DRUDP (HFD-580)
Mike Welch, Ph.D. – Statistician Team Leader, Division of Biometrics II (DBII0 @ DRUDP (HFD-580)
Sue Jane Wang, Ph.D. – Statistician, DBII @ DRUDP (HFD-580)
Margaret Kober – Chief, Project Management Staff, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Health Project Manager, DRUDP (HFD-580)

External Attendees:
Chuck Ebert, Ph.D. - Senior Vice President, Research and Development
Greg Torre, Ph.D. - Vice President, Regulatory Affairs
Steve Sanders, Pharm.D. - Vice President, Proprietary Research and Development
Dorothy Frank, M.S., R.A.C. - Executive Director, Proprietary Regulatory Affairs
Heather Thomas, Ph.D. - Manager, Biostatistics
David Campbell, R.A.C. - Associate II, Regulatory Affairs

Meeting Objective: To discuss with the sponsor the information required to resubmit an NDA for this indication.

Discussion/Decisions Made:

1) **Does the Division agree that the reanalysis of Study O99009 is adequate for one of the two studies requested for approval?**

Response:
No. the Division does not agree since determining adequacy will be a review issue.

Comments regarding the sponsor proposed reanalysis of Study O99009 include:

1) A proposed data reanalysis method has not been discussed with the Division.
2) The Division's decision that Site 12 is to be excluded from the analysis of Study O99009 is unchanged; nevertheless, the Division stated that the reanalysis of study 099009 is probably adequate as one of the two required studies for the purposes of filing, but may not be adequate for substantial evidence.

Request submission of the following:

1) Tabular listing of patient number in Study O99009 for all patients with known incorrect efficacy diary data retrieval/entry, patient site, Visit number and date of visit for any known incorrect/missing diary data, dates of diary data originally submitted for the Visit number with known incorrect/missing diary data, and dates of diary data originally omitted or incorrectly submitted.
2) Submission of copies of all diary data for all patients in Study O99009 with known incorrect/missing diary data retrieval/entry.
3) Tabular listing of all original diary data summaries for all patient in Study O99009 with known incorrect/missing efficacy diary data retrieval/entry.
4) Tabular listing of all revised diary data summaries for all patient in Study O99009 with known incorrect/missing efficacy diary data retrieval/entry.
5) Final Statistical Analysis Plan for Study O99009 and any revisions.

2) **When submitting this amendment, it is Watson's intention to request marketing authorization for the 3.9 mg/day dose [redacted] Does the Division have any feedback regarding this decision?**

Response:

3) **Does the Division agree that Study O00011 is adequate to fulfill the request for a second confirmatory study?**

Response:
No, the Division does not agree since determining adequacy will be a review issue.
Comments regarding Study O00011 include:

1) The Division has consistently recommended that Phase 3 studies intended to support approval of a drug for overactive bladder collect 7 days of patient urinary diary data. The collection of only 3 days of diary data in Study O00011 will be a review issue.
2) The "enriched" study population in Study O00011, by including only patients who have benefited from prior anticholinergic therapy, will be a review issue; nevertheless, the Division stated that study 000011 is probably adequate as one of the two required studies for the purposes of filing, but may not be adequate for substantial evidence.

4) **Does the Division agree that the additional safety data on 39 cm $_2$ Oxytrol systems from Study O00011 to be provided in the amendment obviate the need for the 39 cm $_2$ cumulative irritation study requested by the Division in the non-approvable letter?**

Response:
No, the Division continues to request the 39 cm^2 cumulative irritation study.

5) **Does the Division agree that the planned ISS and subsequent inclusion of this data in the package insert is acceptable?**

Response:
No, the Division does not agree. The ISS should be presented exactly the same as the original NDA. Inclusion of data in the package insert is a review issue. Regarding the Adverse Event Table, the sponsor is referred to the discussion entitled "Tabular Presentation of Adverse Reaction Data" in the DRAFT Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics dated May 2000 (pg. 3-4), which states: Data in the primary table should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative. Data from open-label extension studies may be included in a separate listing (or text) in the ADVERSE REACTIONS section if the medical review team finds it appropriate following review.

6) **Does the Division agree that it is acceptable to make the proposed changes to the label to include the clinical results from Study O00011comparing the Oxytrol 3.9 mg/day system to placebo, the site to site bioequivalence study, inclusion of hip and buttocks as application sites, and as expanded AE table?**

Response:
No, the Division does not agree. It is premature to make labeling agreements. The Division would be willing to review both bioequivalence and wear-study data for the buttock and hip sites in order to support these application sites.

Regarding the Adverse Event Table, the sponsor is again referred to the DRAFT Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics dated May 2000. The sponsor is advised that the Adverse Event Table for Detrol LA reported events exceeding placebo rate > 1% of patients.

7) **Assuming that the information we provide in the pending amendment is adequate, does the Division have any other issues that need to be addressed prior to an approvable action?**

Response:
1) Tabular listing of all investigator sites for Study O00011, number of patients screened at each site, number of patients randomized at each site, and number of patients discontinued at each site.
2) Final Statistical Analysis Plan for Study O00011.

8) **It is our understanding based on FDA's Guidance "Classifying Resubmissions in Responses to Action Letters" that this amendment will be assigned a 6 month user fee goal date. Does the Division agree?**

Response:
Upon receipt of a resubmission to the action letter, the Division will determine whether or not the response is a complete response, thereby restarting the review clock, and the appropriate classification

of the response. If the Division determines that the submission is a complete response and is a Class 2 resubmission, then the submission would be placed on an internal goal date of six months.

Action Items:

- Fax meeting minutes to the sponsor within 30 days.
- The sponsor should submit the requested information in their resubmission of this application.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

MEETING MINUTES

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/s/

Mark S. Hirsch
5/30/02 04:15:52 PM

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Confirmation Report – Memory Send

Page : 001
Date & Time: Mar-26-02 05:46pm
Line 1 : 301-827-4267
Line 2 :
Machine ID : FDA/CDER/OND/ODE3/DRUDP

Job number : 531

Date : Mar-26 05:42pm

To : ☎919733558582

Number of pages : 004

Start time : Mar-26 05:42pm

End time : Mar-26 05:46pm

Pages sent : 004

Status : OK

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Job number : 531 *** SEND SUCCESSFUL ***

FOOD AND DRUG ADMINISTRATION
D SION OF REPRODUCTIVE AND
OGIC DRUG PRODUCTS, HFD-580
JMENT CONTROL ROOM 17B-20
FISHERS LANE
CKVILLE, MARYLAND 20857

DATE: March 26, 2002

Center for Drug Evaluation and Research
FDA

TO: Watson
Name: Greg Tarr
Fax No:
Phone No: 9-1-973-355-8582
Location:

FROM: DRDP
Name: 151
Fax No: (301) 827-4267
Phone No: (301) 827-4260
Location: FDA, Division of Reproductive and Urologic Drug Products

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Comments:

Dear Greg: Attached is the signed action letter for NDA 21-351.

Take care,

151

concurrence:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, Utah 84108-1255

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Campbell:

Please refer to your new drug application (NDA) dated April 26, 2001, received April 26, 2001, submitted under section 505(b) pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Oxytrol (oxybutynin transdermal system) [redacted] 3.9 mg per day.

We also acknowledge receipt of your submissions dated May 11 and 22, June 7, 8, 13 and 27, July 13 and 27, August 3, 9, 10 and 14, September 4, 19, and 27, October 25 and 31, November 5, December 12, 2001, and January 11, 16, and 28, February 7, 12, 14, 15, 27 and 28, and March 13 and 18, 2002, which were reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find that the clinical data presented does not provide sufficient evidence to support safety and efficacy of Oxytrol™ (oxybutynin transdermal sytem) [redacted] 39 cm^2 (delivery rate 3.9 mg per day). Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The specific deficiencies leading to this decision are summarized as follows:

1. The results of the single Phase 3 clinical trial, Study O99009, showed marginal efficacy in the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. A statistically significant difference in the number of episodes of incontinence (the primary endpoint) was demonstrated following treatment with the 3.9 mg per day dose of Oxytrol™ versus placebo. This result, however, was not supported by a second confirmatory study and was not considered compelling. Treatment with the Oxytrol™ 3.9 mg per day dose did not demonstrate efficacy for reduction in urinary frequency, a secondary endpoint in Study O99009. We consider demonstration of efficacy for this parameter clinically important for establishing efficacy in the treatment of patients with overactive bladder.
2. Treatment with the 2.6 mg per day dose of Oxytrol™ did not show a statistically significant result when compared to placebo for either urinary incontinence or urinary frequency.
3. Errors involving the transcription of 35 source document diaries call into question results presented on both doses for the primary and secondary efficacy parameters. Results of a re-analysis of the data following correction of these transcription errors have not been presented to the Agency.
4. There was insufficient safety data collected on skin tolerability for the 39 cm^2 oxybutynin transdermal system.

APPEARS THIS WAY
ON ORIGINAL

To resolve the above deficiencies you should:

1. Submit the results from two randomized, placebo-controlled, clinical trials that provide for each dose of Oxytrol™ (for which approval is sought) substantial evidence of clinical efficacy and safety for the treatment of overactive bladder.
2. Submit a study that assesses cumulative skin irritation and supports the safety of Oxytrol™ 39 cm^2 for the skin

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

Shelley Slaughter
3/26/02 05:30:54 PM
Shelley R. Slaughter, MD., Ph.D. for Daniel Shames, MD

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, UT 84108-1255

APPEARS THIS WAY ON ORIGINAL

Dear Mr. Campbell:

We received your April 19, 2002 correspondence on April 22, 2002 requesting a meeting to discuss the resubmission to the Not Approval Letter dated March 26, 2002. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type A meeting. The meeting is scheduled for:

Date: May 17, 2002
Time: 3:00 PM
Location: Parklawn, 3rd Floor Conference Room "C"

Provide the background information for this meeting at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to hold a meeting, or if we do not receive the package by May 3, 2002, we may need to reschedule the meeting.

APPEARS THIS WAY ON ORIGINAL

If you have any questions, call Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Jennifer Mercier
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

Jennifer L. Mercier
4/24/02 12:58:20 PM

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46 Page(s) Withheld

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

__✓__ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Teleconference Minutes

Date: March 25, 2002 **Time:** 3:30-4:00 PM, EST **Location:** PKLN; 17B43

NDA 21-351 **Drug:** Oxytrol™ (oxybutynin transdermal system)

Indication: overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Notification of regulatory action

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Greg Torre, Vice President, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Shelley R. Slaughter, M.D., Ph.D., Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D., Medical Team Leader, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Chuck Ebert, Senior Vice President, Research and Development
Greg Torre, Vice President, Regulatory Affairs
Steve Sanders, Vice President, Proprietary Research and Development
Dorothy Frank, Executive Director, Proprietary Regulatory Affairs
Cherri Petrie, Associate Director, Proprietary Regulatory Affairs
Kim Caramelli, Principal Scientists, Clinical Research
Heather Thomas, Manager, Biostatistics
David Campbell, Associate II, Regulatory Affairs

Meeting Objective: To convey to the sponsor the Agency's decision regarding the approvability of NDA 21-351.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for systems with oxybutynin — , 3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Discussion:
- DRUDP stated that the objective of this teleconference was to inform the sponsor of the impending action for this application
- review of the data in this application led to a not approvable action, based on the following:

- the results of the single Phase 3 trial showed statistical significance for the primary endpoint of urinary incontinence for the 3.9 mg per day dose; however there was no confirmatory or supporting data and the results are not considered compelling

/

- statistical significance was not demonstrated with either dose for the secondary parameter of urinary frequency, which is important for this indication
- in addition, the data on the primary and secondary endpoints for both doses are in question due to transcribing errors in 35 diaries; the re-analysis of this data has not been received by the Agency
- insufficient data was submitted to adequately assess dermal irritation on the patches for which approval is sought

- in response to the sponsor's questions, DRUDP stated that:
  - the deficiencies noted in the review of this application could not be resolved as Phase 4 commitments and must be resolved prior to approval of this application
  - safety studies to address skin irritation of the 39 cm^2 patch are critical; ; safety studies should include a rigorous assessment of dermal irritation; there is a concern that this may not be the optimal formulation for the oxybutynin transdermal patch
  - re-analyis of the data discrepancy from the 35 diaries with transcription errors may be submitted in the next review cycle
  - DRUDP will require a new confirmatory trial, even if the re-analysis of the data discrepancy shows improvement in the statistical analysis
  - total exposure in humans was considered borderline, but this was not deemed to be an approvability issue
  - data for this novel oxybutynin formulation must show compelling evidence for efficacy and safety from two trials; the required safety and efficacy data must be derived from two studies which are confirmatory of each other; DRUDP can't determine at this time, without reviewing the data, if the sponsor's Detrol LA study is a confirmatory study sufficient for approval
  - administratively, the sponsor should inform DRUDP of its future plans for this application as outlined in the action letter
  - the sponsor should follow the meeting request guidelines for any future meetings; the topic of immediate meetings should be limited to the resolution of the not approvable issues; discussions on pediatric studies should be postponed
  - pooled analysis of two trials is not acceptable
- the sponsor clarified that DRUDP had indicated previously that it was too late in the review cycle for submission of the re-analysis data

Decisions made:

- DRUDP determined that upon review of the data submitted by the sponsor NDA 21-351 is not approvable

Action Items:

- DRUDP will send a regulatory letter to the sponsor on March 26, 2002, notifying the sponsor of the Division's not approvable decision for this application
- Watson Laboratories will notify DRUDP of its plans for Oxtyrol™ future development within ten days of receipt of the regulatory letter

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Drafted: Farinas 3.26.02
Concurrence: Kober 3.29.02/Hirsch 4.3.02/Slaughter 4.23.02
Finalized: Farinas 4.25.02

MEETING MINUTES

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/s/

Evelyn Farinas
4/26/02 11:41:33 AM
CSO

Shelley Slaughter
4/29/02 12:44:05 PM
MEDICAL OFFICER
I concur.

6 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Roy Blay
DSI

Facsimile Transmittal

4-0747

To:	Dr. Gierhart	**Fax:**	[Click here and type fax number]
From:	Roy	**Date:**	03/05/02
Re:	Dr. Feagins	**Pages:**	7 (inc. cover)
CC:	[Click here and type name]		

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Per your request. Please let me know if you need anything else.

Roy

CONFIDENTIAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Brian A. Feagins, M.D.
Urology Clinics of North Texas
8210 Walnut Hill Lane, Suite 208
Dallas, Texas 75231

MAR - 1 2002

Dear Dr. Feagins:

Between April 9 and May 3, 2001, Mr. Phillip D. Waldron and Ms. Kelly J. Pegg, representing the Food and Drug Administration (FDA), met with you to review your conduct of the following clinical study:

> Protocol #099009 "Transdermal Oxybutynin in Patients with Urge Urinary Incontinence: A 12-Week Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study with a 12-Week Open-Label, Dose-Titration, Safety Extension", involving the investigational drug transdermal oxybutynin, performed for Watson Laboratories, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your response dated February 14, 2001, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We note that at the conclusion of the inspection, Mr. Waldron and Ms. Pegg presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. Your letter of February 14, 2001, satisfactorily explains the inspectional observations listed in the Form FDA 483, except for the following:

1. You failed to personally conduct and supervise the clinical investigation in that study records for subjects 1213 and 1214 contain misrepresented data.

   a. Subject 1213's electrocardiograms (EKGs) dated — (Visit 7) and — (Visit 10) are identical.

   b. Subject 1214's EKGs dated — are identical.

   c. You confirmed that your signature on the case report forms (CRFs) was forged and that you did not perform the Visit 3 physical examinations.

   You informed us that you conducted your own internal investigation into these discrepancies and found that certain computer software used by your staff could also be used to alter ECG reports. You also informed us that as part of the investigation, subjects 1213 and 1214 were interviewed and they stated that they each had only one ECG performed throughout their participation in this study, despite the presence of multiple ECGs in their study records. While much of the evidence suggests that a member of your staff may have created these

misrepresentations, we remind you that as principal investigator you are ultimately responsible for the study related duties of your study staff, including study coordinators.

2. You failed to maintain adequate and accurate records and case histories in that electronic progress notes do not accurately reflect the information reported on CRFs. For example:

   a. The electronic progress note of 7/20/00, for subject 1208, does not include the physical examination findings to support entries in the CRF. We specifically note that there was no documentation indicating that the CRF was the source document in this case.

   b. The progress note of 7/26/00, for subject 1217 indicates that the subject was seen by you; however, there are no source documents to support that the physical examination reported on a CRF page containing the sub-investigator's signature was performed by you or the sub-investigator at this visit. We note that there was no documentation indicating that the CRF was the source document.

   We note that there was no consistent procedure for documenting data. You used CRFs as a source document for physical examinations, and your staff would subsequently enter these findings into electronic progress notes. One sub-investigator entered the physical examination data directly into the electronic progress notes while other sub-investigators dictated their findings for transcription. Thus, we are unable to determine in all instances which records served as source documents. We wish to remind you that whichever method you choose to record data, your staff must consistently use this method at all times and comply with 21 CFR 11.10.

3. You failed to adhere to the requirements for an electronic record keeping system in that you did not employ procedures and controls to ensure (a) the authenticity, integrity, and when appropriate, the confidentiality of electronic records; and (b) that the signer of the electronic record cannot readily repudiate the signed record as not genuine. We specifically note that you failed to include the following procedures and controls:

   a. Regarding systems validation, you failed to validate the accuracy, reliability, and consistent intended performance of the electronic systems used to collect study data. In addition, you failed to validate the ability of these systems to discern invalid or altered records.

   b. Regarding audit trails, you failed to use secure, computer-generated, time-stamped audit trails to independently record the time and date of operator entries and actions that create, modify, or delete electronic entries. We note that for all of the subjects enrolled in this study, at least some progress notes, including some physical examination findings, were routinely left open (not electronically signed) for extended periods, enabling changes without an audit trail. In certain cases (subjects 1203, 1204, and 1208), electronic signatures were not added to electronic progress notes until approximately one year after these records were originally created. Because of these electronic record-keeping inadequacies, we are unable to determine what revisions were actually made to study

records prior to their closure by electronic signature.

c. Regarding written policies, you failed to establish and adhere to written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures.

4. You failed to adhere to the requirements for electronic records and signature manifestations by not ensuring that all signed electronic records indicate the time when the signature was executed and the meaning (such as review, approval, responsibility or authorship) associated with the signature.

5. You failed to maintain adequate drug accountability in that there were discrepancies between the electronic progress note and the corresponding CRF for subject 1211. The progress note indicates that five quantities of study drug were returned, while the CRF shows seven quantities returned.

We acknowledge your response and accept your assurance that corrective actions will be taken to prevent similar problems in your current and future studies. Your letter will be added to your file. If information is requested from your file in accordance with the Freedom of Information Act, our response will include all the related correspondence in your file.

Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practices I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

FEI: 3003324937
Field classification: OAI
Headquarters classification:
___1) NAI
___2) VAI – no response required
___3) VAI – response requested
_X_4) VAI-RR – response received
___5) OAI – WL 15 day response
The ECG date falsifications were done using a scanner and optical character recognition software by a professional computer expert. It is unreasonable to expect the principal investigator to uncover the falsified dates on ECG even with adequate supervision because the PI was not required to prepare ECGs. The PI promptly investigated and took corrective actions to rectify the problem.

Deficiencies noted:
_____inadequate consent form
__x__inadequate drug accountability
_____failure to adhere to protocol
__x__inadequate records
_____failure to report ADRS
__x__other: (Failure to adequately supervise [21 CFR 312.60 and 312.53(c)(1)(vi)(c)]
Electronic recordkeeping violations (21 CFR 11.10, 11.30 and 11.50)
Deficiency codes: #4, #6, #18
cc:
HFA-224
HFD-013 (FOI)
HFD-580 Doc. Rm.: NDA #21-351
HFD-580 MO/Gierhart
HFD-580 PM/Farinas
HFD-46 files w/original records, GCP file #10375
HFD-46 GCPI /U/Blay
HFD-340 r/f
HFR-SW150 DIB/Thornburg
HFR-SW1540 BIMO Monitor/Martinez
HFR-SW150 Field Investigators/Waldron/Pegg
HFC-230
HFD-300

r/d:/cl:12.02.01; rs:/ 2.02.02
reviewed:/jm:/12.3.01
reviewed:/kmu:/ 2.11.02; 2.22.02
reviewed:/rab/2.22.02;2.28.02
reviewed:/aeh:/2.7-2.10.02; 2.22.02
f/t:jau:/12.12.01; sg:/2.25.02; 2.27.02; 3/1/02
o:/ blay/feagins.doc

Gierhart, Brenda S

rom: Farinas, Evelyn R
Sent: Thursday, February 28, 2002 10:51 AM
To: Gierhart, Brenda S
Cc: Farinas, Evelyn R
Subject: FW: request for information

Reply from David Campbell, Watson laboratories/Oxytrol

Evelyn
-----Original Message-----
From: DCampbell@Watsonpharm-FDA.COM [mailto:DCampbell@Watsonpharm-FDA.COM]
Sent: Thursday, February 28, 2002 10:26 AM
To: Farinas, Evelyn R
Cc: dfrank@watsonpharm-FDA.com
Subject: Re: request for information

Evelyn,

Reference is made to the 02/11/02 e-mail in which FDA requested resolution of two data discrepancies that were noted by the medical reviewer in comparing the submitted database to notes om their field auditor during the site audit at Dr. Antoci's site (Site # 03). Watson has reviewed ıese issues and has the following response:

Patient 0304: The first issue involved the Visit 7 urinary diary for patient 0304. The data listing in the NDA contained 6 days of diary data, with missing data from Day 5 (04/15/00), however, the auditor identified a complete 7 days of recordings in the diary at the site.

Findings: The CRFs were retrieved and a copy of the diary was examined. There was no Day 5 page in the CRF copy. The site was contacted and confirmed that a Day 5 page existed in the original diary. This page was faxed to Watson. The page indicated 10 normal voids and no incontinence episodes; voided volumes were not recorded on this day. These data are consistent with the summary data presented for this visit (2 incontinence episodes, urinary frequency = 10).

Conclusion: The Visit 7 diary of patient 0304 did contain 7 days of recording while only 6 days were included in the database used for study analysis. The patient was in the placebo treatment group. For the primary outcome variable, since there were no incontinence episodes on the missing day, the scaled data (7/6 x # episodes) would remain 2 episodes. This omission has no anticipated impact on study results.

Implications for Additional Discrepancies: To explore the possible incidence of this type of data entry discrepancy in other diaries, we generated a listing of all diaries that contained fewer than 7 days of data for any diary period. This list included 111 diaries. A complete review was made of ·se diaries. Of these, 80 were correct as entered (database and CRF diary records consistent). Ten) were identified as having missing pages. Of these 10, 9 had a single page missing, 1 had 4 pages .ıissing. Records at the investigator's sites would have to be reviewed to resolve whether data exist or not for these days. The remaining 21 diaries were all provided to — as double-sided copies. During the data entry process, it appears that only one side of the page was entered. The distribution

of treatment groups in all 31 diaries included: placebo group, 10; 13 cm^2 group, 4; 26 cm^2 group 9; and 39 cm^2 group 8. This relatively even distribution between indicates a minimal potential impact on study outcome.

Patient 0325: The second FDA query regarded a repeat baseline diary for patient 0325. The database indicated diary dates for the baseline evaluation during the initial diary record, despite the documentation that the patient had a repeat diary. The repeat diary data should have been used in the database.

Findings: We confirmed that the original diary was erroneously used as the baseline diary. It appears that only the original diary was sent to [redacted] There was no copy of the second diary in the CRFs, however, the site confirmed that they had the second diary and faxed a copy of it to Watson. In this case, the two diaries were discrepant in the number of episodes recorded. During the initial diary, 80 episodes were recorded in 5 days; 48 episodes were recorded in the second diary over 7 days.

Conclusion: Since the second diary had fewer episodes, the change from baseline (primary outcome variable) is greater using the initial diary, leading to falsely elevated change for this patient. Since this patient was in the 26 cm^2 treatment group, the impact on study interpretation would be minimal as this dosage strength did not result in a significant difference from placebo for the primary outcome variable.

Implications for Additional Discrepancies: To explore the possible incidence of this type of data entry discrepancy for other patients, the dates of the 87 repeat baseline diaries, as identified in the clinical study report and database, were examined. We examined the data listings to determine whether or not the correct data (2nd diary) were entered in these 87 cases. In 4 cases, including patient 0325, the second diary was not correctly used as the baseline. In one case, no repeat diary record is included in the CRF. Further clarification would require contact with the investigator to determine if the original records include the repeat diary. In the other two instances the second diary was available for review. The table below outlines the data for the first and second diaries for these four cases.

ID	Episodes/diary days		Treatment
	1st diary	2nd diary	
0325	80/5	48/7	26 cm^2
1133	9/7	11/7	13 cm^2
2023	14/7	23/7	Placebo
2412	19/7	No diary	13 cm^2

Overall Conclusion: Although 25 diary errors have been detected (with the potential for a total of 35 errors), the error rates are very low and represent a small portion of the overall data. Approximately 500 diaries were collected in the study yielding an estimated error rate of approximately 1% - 1.4% (25 or 35/2500). In addition, the distribution is relatively even over the treatment groups. It is doubtful that any change in the interpretation of the study results would occur with correction of these

errors.

.lthough we feel that the impact of these discrepancies are minor to the outcome of the primary analysis, Watson is re-evaluating the analysis using the corrected diary data. and would be able to provide revised data tables to the Division if requested.

I'll follow this e-mail with a hard copy submission to the NDA.

Best Regards,

David

APPEARS THIS WAY
ON ORIGINAL

"Farinas, Evelyn R"
<FARINASE@cder.fda.gov>

02/11/2002 02:24 PM

To: "'dcampbell@watsonpharm-FDA.com'" <dcampbell@watsonpharm-FDA.com>
cc: "Farinas, Evelyn R" <FARINASE@cder.fda.gov>
Subject: request for information

'avid:

'he Medical Officer requested that I forward this request:

Please resolve the following two data discrepancies regarding the urinary diary data submitted to NDA 21-351 at Dr. Joseph P. Antoci's site:
Subject #0304: Study records for urinary diary data reported by the subject on April 15, 2000 (Day 5 of endpoint week) were noted during site inspection; this data was not located in the NDA 21-351 data listing in Volume 70 for Subject #0304 at Visit 7 on pg. 106-109.
Subject #0325: Baseline urinary diary data was reported in NDA 21-351 Volume 70 for Visit 3 on pg. 293-298 as having been obtained from February 21-27, 2000. However, study records indicate that the subject was rejected for randomization on February 28, 2000, because the subject did no complete Days 6 and 7 of the diary correctly. The subject repeated the screening diary between February 29 and March 7, 2000 and was approved for randomization on March 7, 2000. The baseline data collected between February 29 and March 7, 2000 was not located in the NDA 21-351 data listing in Volume 70 for Visit 3 on pg. 293-298.

We would appreciate a quick response.

Thanks for your help as always,

Evelyn

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: Gregory M. Torre, Ph.D.
Vice President, Regulatory Affairs
417 Wakara Way
Salt Lake City, UT 84108

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Torre

We received your February 13, 2002 correspondence on February 13, 2002, requesting a meeting to discuss the implications of a recently completed phase 3B study on the review of NDA 21-351. We considered your request and concluded the meeting is premature because review of your application is ongoing.

We remind you of the February 14, 2002, teleconference between Ms. Frank and Ms. Farinas, where the above information was conveyed to you.

We also remind you of our letter of February 6, 2002, indicating that the Division would contact Watson Laboratories to schedule a teleconference at a later time, if necessary, to discuss any pending questions or concerns relating to this NDA.

If you disagree with our decision, you may discuss the matter with Evelyn R. Farinas, Regulatory Project Manager, at 301-827-4260. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

APPEARS THIS WAY
ON ORIGINAL

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

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/s/

Daniel A. Shames
2/22/02 01:49:30 PM

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ON ORIGINAL

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ON ORIGINAL

APPEARS THIS WAY

Teleconference Minutes

Date: February 12, 2002 **Time:** 2:15-2:25 PM, EST **Location:** PKLN; 17b-45

NDA 21-351 **Drug:** Oxytrol **Indication:** overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Chemistry guidance

Meeting Chair: Rajiv Agarwal, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Lead: Dorothy Frank, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Rajiv Agarwal, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Dorothy Frank – Executive Director, Proprietary Regulatory Affairs
Ray Coates – Executive Director, Quality Operations
Joe Baker- Executive Director, Technical Operations
Mamum Khan – Director, Analytical Services
Scott Gouchnor – Director, Technical Services
Jill Callahan – Manager, Technical Services Administration
David Campbell – Associate II, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

Meeting Objective: To obtain clarification on Watson's responses to the December 6, 2001, Discipline Review Letter.

Background: In correspondence dated January 11, 2002, Watson provided responses to the Division's Discipline Review Letter of December 6, 2001, which listed Chemistry deficiencies uncovered during this NDA review.

Discussion:

- the sponsor was reminded that the acceptance criteria for [redacted] is rather generous; per ICH-Q3A this impurity should be qualified and identified; the sponsor was asked to submit the structure of this impurity
  - the sponsor agreed to submit the requested information
- the sponsor was asked to identify the [redacted] addressed in deficiency #10
  - the sponsor indicated that the [redacted] was standard pharmaceutical grade [redacted] material

- the sponsor was informed that the Division had not received a response from the holder of DMF [redacted] if the information required is not received on time, the sponsor may have to exclude this facility
  - the sponsor stated that despite requests to [redacted] for a quick response, no time frame could be provided at this time for a reply from [redacted]
  - the sponsor will continue to work with [redacted] to expedite a response to the Division

Decisions made:

- the sponsor will submit the structure of the [redacted] and the [redacted] showing the structure of [redacted]
- the sponsor will exclude DMF [redacted] if the responses to DMF deficiencies do not reach the Agency in a timely fashion

Action Items:

- the sponsor will submit the structure of the [redacted] ia facsimile as soon as possible
- minutes will be sent to the sponsor within 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

Rajiv Agarwal
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Status Meeting Minutes

Date: January 31, 2002 **Time:** 9:00-10:00 AM, EST **Location:** PKLN; 17B-43

NDA 21-351 **Drug:** oxybutynin transdermal system **Indication:** Overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Status

FDA Attendees:
Daniel Shames, M.D. – Acting Director, Division of Reproductive and Urology Drug Products (DRUDP; HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Young-Moon Choi, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D.- Pharmacokinetics Team Leader OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for this NDA.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for systems with oxybutynin delivery rates of —— 3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor also submitted the tradename "Oxytrol" for OPDRA's consideration. Relevant meeting dates for this application are: November 10, 1999 for the End of Phase 2 meeting (IND 50,489); December 8, 2000 for the pre-NDA meeting; and June 13, 2001 for the filing meeting. The PDUFA goal date is February 26, 2002. The internal goal date for submission of the Action Package to the Division Director is February 12, 2001.

Discussion:
General discussion:
- ODE III approved extending the review clock for this application, due to existing workload; the revised goal date is March 26, 2002
- the sponsor will be informed about the revised goal date
- the sponsor will be informed that the Division will contact them for further discussion; the Division will provide questions and/or issues for discussion via facsimile prior to the discussion date

Clinical:
- review ongoing
- issues:

- regarding efficacy: 26-cm patch efficacy results are worse than placebo in the one phase 3 trial; data does not support the efficacy of the 26-cm patch; 39-cm patch efficacy results did not show improvement over placebo in the urinary frequency endpoint if Site #12 was excluded and minimal efficacy for urinary incontinence endpoint was shown; Study 096017 had several problems: it was underpowered, the patches tested (13-, 26-, 39- and 52-cm patches) in this study did not demonstrate equivalence to the oral dose
- regarding safety: very small number of patients were dosed with the 39-cm patch; the data may be adequate, but it is concerning that one site will be excluded due to DSI recommendation, and another appears to have inaccurately transcribed data; comparison of adverse events frequency between the patch and the oral dose, may not be possible because the amount of oxybutynin released from the patch is less than the oral dose

- assessment: a non-approval action is being considered

Chemistry:

- review on going
- issues:
  - regarding CMC deficiencies: a response from the sponsor to previously identified CMC deficiencies is under review; it appears that the sponsor accepted DRUDP's recommendations
  - regarding DMF deficiencies: Deficiencies were identified and communicated to the three DMF holders; responses from two are under review; the response from the third DMF holder — is pending
  - regarding inspections: one foreign site inspection is still pending
- labeling: DRUDP reviewer agrees with the Division of Drug Marketing, Advertising and Communication (DDMAC) comments; the name listed by the sponsor in the patient package insert is not acceptable; the backing film is not clearly described in the how supplied section; the cartons for the — have not been submitted
- assessment: approval pending resolution of the issues listed above

Clinical Pharmacology and Biopharmaceutics:

- review on going
- issues:
  - additional consultation with the Chemistry reviewer is needed to set the dissolution specifications
  - release specifications need further review
  - system exposure comparison with oral Ditropan does not demonstrate comparable exposure; lower efficacy may be due to lower metabolite concentration; comparability with oral dosage is not possible
  - the reviewer stated that there was no significant gender effect, no population PK issues, and no food effects
- labeling: confidence intervals were met in all of the three application sites proposed by the sponsor, and thus the label may indicate three application sites
- assessment: data is acceptable, with comments to be provided to the sponsor

Toxicology:

- review on going
- no issues at this time
- labeling is being reviewed
- assessment: recommend approval

Statistics: (conveyed through the Medical Officer)

- review on going
- issues:
  - the median response in the oxybutynin 39-cm^2 TDS group in Study 9009 for episodes of urinary incontinence was marginally statistically significant, and no consistent statistical evidence was observed among the secondary outcomes
  - Study 9007 failed to conclude in responder rate that oxybutynin TDS was equivalent to oral oxybutynin and an unplanned interim statistical analysis was conducted by the sponsor

Decisions made:

- the review clock for NDA 21-351 has been extended to 11 months, with a March 26, 2002, revised goal date
- the sponsor will be provided an opportunity for dialogue and discussion of pending issues at a later date, prior to the revised goal date

Action Items:

- Project Manager to contact the sponsor for an update on the status of the pending DMF holder response — *has not responded to Watson's inquiries regarding the status of their responses to the deficiency letter from the Division, per David Campbell, via telephone conversation on January 31, 2002*)
- Project Manager to contact the sponsor for clarification regarding the missing carton information (*the sponsor will* [redacted] *per telephone conversation with David Campbell, Watson's Associate II, Regulatory Affairs, on January 31, 2002*)
- Clinical Pharmacology and Biopharmaceutics reviewer to provide copies of draft review to Medical Team Leader and Medical Officer
- Project Manager to inform the sponsor of the revised goal date and of the opportunity for dialogue and discussion at a later date (*Dorothy Frank, Watson's Regulatory Affairs Director, was informed via telephone on January 31, 2002, that: the review clock was extended to 11 months; the Division is amenable to a teleconference at a later date for further discussion; items for discussion will be faxed to the sponsor prior to the teleconference date; and that scheduling of the teleconference will take place at the time when items for discussion are sent to the sponsor*)

Drafted: Farinas/ 2.11.02
Concurrence: Best 2.13.02/Moore; Hirsch 4.26.02 /Gierhart 2.12.02/Agarwal /Wang / Choi/Parekh 2.12.02
Finalized: Farinas/ 4.26.02

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/s/

Mark S. Hirsch
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: Gregory M. Torre, Ph.D.
Vice President Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

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Dear Dr. Torre:

We received your January 28, 2002, correspondence on January 29, 2002, requesting an expedited telephone conference on February 15, 2002, or during the first two weeks in February, to discuss any questions the Division may have concerning this application. We considered your request and concluded that the meeting is premature because review of your application is still on going at this time.

We remind you of the January 29, 2002, telephone conversation between you and Ms. Farinas, where the above information was originally conveyed to you.

We also remind you of the January 31, 2002, telephone conversation between Ms. Dorothy Frank and Ms. Farinas, where Watson Laboratories was informed that the Division would contact Watson Laboratories to schedule a telephone conference at a later time, if necessary, to discuss any pending questions or concerns relating to this NDA. During the January 31, 2002, telephone conversation, Ms. Frank was also informed that the Division had extended the PDUFA goal-date to 11-months for the first review cycle of this NDA. The additional one month is necessary to complete this application's review.

If you disagree with our decision, you may discuss the matter with Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled "Formal Dispute Resolution: Appeals Above the Division Level (February 2000)". The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
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For Terri Rumble

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Internal Meeting Minutes

NDA: 21.351 **Drug:** Oxytrol (oxybutynin transdermal system ~~—~~ 3.9 mg/day)

Date: January 7, 2002 **Time** 11:00 AM – 12:00 PM

FDA/CDER/DRUDP Attendees:
Meeting Chair: Mark Hirsch, Medical Team Leader
Dan Shames, DRUPD Division Director
Donna Griebel, DRUPD Deputy Division Director
Meeting Recorder: Margie Kober, Chief Project Manager
Rajiv Agarwal, Chemist
Ameeta Parekh, Clinical Biopharmaceutics

Background: This was the 5-month internal team meeting to discuss status of ongoing reviews for this resubmitted NDA.

Issues discussed/Decisions Made:

1. The team summarized the issues that resulted in the previous not approved action on this NDA. In summary, the two lower doses were ineffective; the highest dose was effective for incontinence, but not urinary frequency; the sponsor submitted only one clinical study for the original NDA; and because of the large size of the transdermal patch, an irritation study was needed.

2. **Internal Team goal dates also discussed at this meeting include**:

   February 1, 2003: begin label discussions with Watson Labs
   February ~, 2003: Action packet to Team Leader, Dr. Mark Hirsch
   February 21, 2003: Action packet to Director, Dan Shames
   February 28, 2003: PDUFA Action packet due date

3. Clinical discussion: First draft of review was given to Medical Team Leader on December 24, 2002. The new study (Protocol 000011) failed on frequency. The significance of this continues to be subject of ongoing clinical review. Awaiting final Biometrics memo.

4. Biopharmaceutics discussion: Review is ongoing, with particular focus on the review of the adhesion data and delivery rate information from the irritation studies. The reviewer noted that if the same exact site is used repeatedly, exposures are higher than if sites are alternated. In the clinical trial, sites were alternated and the label recommends site alteration. A modified OCPB briefing will be held.

5. CMC: No CMC issues noted in first review cycle. Labeling has been modified. DMETS Consult is pending regarding container and carton labels and re-check of tradename. Sites are acceptable. Stability is acceptable at ~~24 months~~.

6. **The schedule for the next internal team meeting (5.5 month status meeting):** Tuesday, January 28, 2003 11:00 AM-12:00 PM.

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/s/

Mark S. Hirsch
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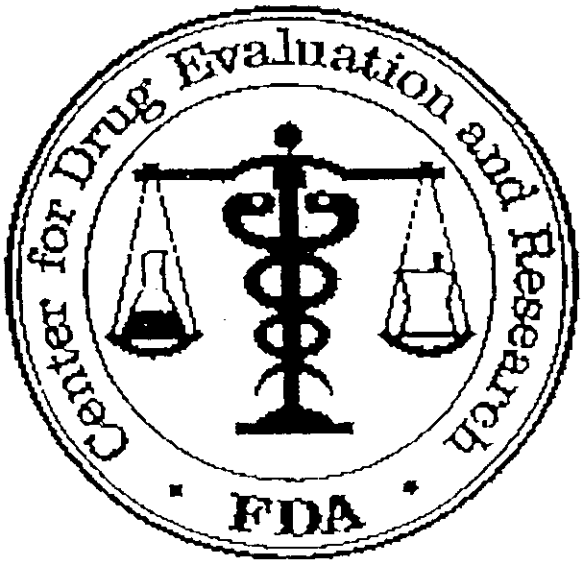
'OOD AND DRUG ADMINISTRATION
'VISION OF REPRODUCTIVE AND
.OLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: Jan 2 | 02



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TO: Watson

Name: David Campbell

Fax No:

Phone No: 9:1-801-583-8175

Location:

FROM: DRUDP

Name: 51

Fax No: (301) 827-4267

Phone No: (301) 827-4260

Location: FDA, Division of Reproductive and Urologic Drug Products

Comments:

Dear David. Attached are the comments and questions posed by Dr. Gerhart.

My best wishes to you and Dorothy in 2002.

Take care.

51

concurrence:

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January 2, 2002

Dear David:

The Medical Officer for your pending NDA for Oxytrol, NDA 21-351, has these two requests:

1. Table 14.3.5.1.4.2 in the 120-Day Safety Update Report in Volume 1 on pages 000456-000459 makes it difficult to interpret total exposure for at least 26 or 52 weeks since the interval (weeks) provided was as (x,y] =total exposure between (exclusive) and y (inclusive). For example, exposure for the interval (25,26] could have included subjects exposed for less than 26 weeks total exposure. Using the most conservative estimate of the information provided, a total of 137 patients were exposed to treatment at any dose for at least 6 months (i.e. 26 weeks or more) and 57 patients for at least 12 months (i.e. 52 weeks or more). A total of 46 patients were exposed to the 26 cm^2 dose for at least 6 months and no patients were exposed to the 26 cm^2 dose for at least 12 months. A total of 64 patients were exposed to the 39 cm^2 dose for at least 6 months and 1 patient was exposed to the 39 cm^2 dose for at least 12 months. Please confirm that these numbers are correct.

2. Please provide a listing by patient number for all patients whose total exposure to study drug at any dose level was at least 52 weeks, broken down by how many complete weeks of exposure occurred at each dose level, for example:
Patient 1109 was exposed to Oxybutynin TDS for a total of at least 11 weeks at the 13 cm^2 dose level, at least 22 weeks at the 26 cm^2 dose level, and at least 18 weeks at the 39 cm^2 dose level, for a total of at least 53 weeks at any dose level.

As always, thanks for your prompt reply to our questions and requests.

Take care,

Evelyn

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 11 2001

Joseph P. Antoci, M.D.
160 Robbins Street
Waterbury, Connecticut 06708

Dear Dr. Antoci:

Between October 15 and 18, Mr. Anthony C. Warchut, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #099009) of the investigational drug oxybutynin transdermal system, performed for Watson Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Warchut during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

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FEI: 3002270571
Field Classification: NAI
Headquarters Classification:
__X_ 1) NAI
_____2) VAI- no response required
_____3) VAI- response requested
_____4) OAI

Deficiencies noted: None

cc:
HFA-224
HFD-580 Doc.Rm. NDA #21-351
HFD-580 Review Div.Dir./Allen
HFD-580 MO/Gierhart
HFD-580 PM/Farinas
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File #10152
HFD-46 GCP Reviewer/Lewin
HFD-46 GCPI Br Chief/Martin
HFD-46 CSO/Ibarra-Pratt
HFR-NE252 DIB/Kravchuk
HFR-NE250 Bimo Monitor/Kelley
HFR-NE2530/Field Investigator/Warchut

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reviewed:JM:12/11/01
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Note to Rev. Div. M.O.

This routine clinical inspection was conducted in support of pending NDA #21-351 and focused on the conduct of protocol #099009.

Twenty-three subjects were randomized at this site, 20 of whom completed the double-blind portion of the study. One subject was withdrawn after improperly being enrolled with exclusionary criteria; two other subjects withdrew due to adverse reactions to the skin patch.

Records for all subjects were reviewed. Inspection revealed that Dr. Antoci appears to have conducted the study in compliance with FDA regulations; no Form FDA 483 was issued.

However, please note that inspection revealed certain discrepancies between source data and the data listings that the sponsor submitted to DSI for use in the inspection. No explanation for these discrepancies was identified at this clinical site. Specifics are as follows:

A. Comparison of the adverse-event data listing supplied by the sponsor to the raw data at the site found that there were two serious adverse events (SAEs) and a number of non-serious AEs that were appropriately reported to the sponsor on case report forms (CRFs) but not included in the sponsor's data listing submitted to DSI:

1. Subject 0318
   a. SAE: Hospitalization from November [redacted], for profound bradycardia (35 to 40 bpm). The bradycardia was considered related to treatment for pre-existing multiple sclerosis, which had flared up approximately two weeks prior to admission.
   b. AEs: CRF notes exacerbation of multiple sclerosis from [redacted], Lyme disease starting [redacted], and noted to be continuing on a [redacted] source document; and insomnia and constipation, both of which began [redacted], and were reported on a June 1, 2001, source document as continuing. All of these AEs were considered unrelated to study drug. In addition, CRF notes AE of dry mouth from [redacted] which was considered possibly related to study drug.
2. Subject 0330
   a. SAE: Hospitalization from [redacted], for left-sided weakness that was determined to result from a cerebrovascular accident (CVA). The CVA was considered unrelated to study drug.
   b. AEs: CRF notes premature ventricular contractions (PVCs), urinary tract infection (UTI), elevated hyaline casts, and memory loss secondary to the CVA noted above. The PVCs began [redacted], and were reported on a [redacted], source document as continuing; reportedly, no treatment was required. The UTI occurred from [redacted] and was treated with medication. The memory loss began [redacted], and was reported on a June 1, 2001, source document as continuing. All of these AEs were considered unrelated to study drug.
3. Subject 0303 – CRF notes elevated cholesterol that began on [redacted] and was reported on a June 1, 2001, source document as continuing. This AE was considered unrelated to study drug.
4. Subject 0305 – CRF notes right eye and right knee injuries and diarrhea. The eye and knee injuries were reportedly sustained in a fall and resolved without treatment. The diarrhea reportedly occurred from [redacted], and was treated with medication. All of these AEs were considered unrelated to study drug.
5. Subject 0306 – CRF notes elevated triglycerides that began on [redacted] and was reported on a June 1, 2001, source document as continuing. This AE was considered unrelated to study drug.
6. Subject 0308 – CRF notes open-angle glaucoma and ankle edema. The glaucoma, which was considered unrelated to study drug, reportedly began on [redacted].

— and was reported on a June 1, 2001, source document as continuing. The ankle edema, which was considered possibly related to study drug, reportedly began on — and resolved on — Both of these AEs were treated with medication.

7. Subject 0321 – CRF notes cloudy urine with moderate amount of bacteria starting — and reported on a June 1, 2001, source document as continuing. This AE was considered unrelated to study drug.
8. Subject 0324 – CRF notes exacerbation of depression from — , and hypertension from — . Both of these AEs were treated with medication and were considered unrelated to study drug
9. Subject 0325 – CRF notes cloudy urine with moderate amount of bacteria starting — , and reported on an April 12, 2001, source document as continuing. This AE was considered unrelated to study drug.
10. Subject 0327 – CRF notes elevated cholesterol, triglycerides and GGT that began on — and were reported on an April 12, 2001, source document as continuing. These AEs were considered unrelated to study drug.
11. Subject 0334 – CRF notes broken right knee cap, which occurred on — and urethral caruncle which started on — . Both of these AEs, which were considered unrelated to study drug, reportedly were treated with medication and were documented in an April 12, 2001 source document as continuing events.
12. Subject 0336 – CRF notes UTI symptoms from — , which were reportedly of mild intensity and which were considered probably related to study drug. In addition, CRF notes elevated GGT, considered unrelated to study drug, starting — , and noted on a June 1, 2001, source document as continuing event.

B. Other data discrepancies:

1. Subject 0304 – Urinary diary data reported by the subject on April 15, 2001 (Day 5 of endpoint week) was not captured in the sponsor's data listing submitted to DSI. All of the April 15, 2001, diary entries pertain to normal voids (total of ten) experienced by the subject after awaking at 7:50 a.m.; there are no post-bedtime entries noted.
2. Subject 0325 – Baseline urinary diary data is reported in the sponsor's data listing as having been obtained from February 21 – 27, 2000. However, study records indicate that the subject was rejected for randomization on February 28, 2000, because the subject did not complete Days 6 and 7 of the diary correctly. The subject repeated the screening diary between February 29 and March 7, 2000, and was approved for randomization on March 7, 2000. The baseline data collected between February 29 and March 7, 2000, is not included in the sponsor data listing provided for the inspection.

The review division may wish to consider the impact of the above discrepancies on the acceptability of the sponsor's data.

Data from this site appears acceptable.

Meeting Minutes

Date: December 10, 2001 **Time:** 11:00 – 12:00 PM **Location:** 17B-43

NDA: 21-351

Indication: Treatment of patients with overactive bladder with symptoms of urge urinary incontinence urgency and frequency.

Sponsor: Watson Laboratories, Inc.

Meeting Type: Status Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Raj Agarwal, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Sue Jane Wang, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)
Young Choi, Ph.D. – Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB (HFD-870)
Jennifer Mercier – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for this NDA.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for _____ 3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor also submitted the tradename "Oxytrol" for OPDRA's consideration.

Discussion:
Clinical:
- The clinical review is in progress.
- The Division will re-calculate the data without Dr. Fagin's results because of a Warning Letter that will be issued form the Division of Scientific Investigation (DSI).
- The sponsor will submit a revised Pediatric Plan this week.

- The label is under review.
- The sponsor has submitted the safety update with information on 80 patients.
- There are patch application problems specifically partial detachment.

Clinical Pharmacology and Biopharmaceutics:

- The review is in progress.
- The Wear study appears to demonstrate a site and size dependency; there is an issue of partial detachment with the patch.
- If the sponsor wants to use all three sites in the label, then they need a statement in the label

Chemistry:

- The Division issued an Information Request (IR) letter on December 6, 2001.
- The DMF for this NDA has deficiencies that will need to be rectified prior to the action date.
- The patch is adhering to the pouch; this is a potential concern for the Division.
- The site inspections are still pending for France and Japan.
- The label is under review.

Microbiology:

- The Division of Microbiology agrees with the sponsor that there is no need for setting specification because

Statistical:

- The draft review is complete and will be sent to the Team Leader.
- The review has been done excluding Dr. Fagin's data since there was a for-cause inspection.

Action Items:

- All reviews need to be completed.
- Labeling revisions should be made to the label on the N drive.

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Mark S. Hirsch
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

DISCIPLINE REVIEW LETTER

Watson Laboratories, Inc.
Attention: David Campbell
417 Wakara Way
Salt Lake City, Utah 84108-1255

Dear Mr. Campbell:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food Drug, and Cosmetic Act for oxybutynin transdermal patch.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. A specification for the — in the drug substance, which is supplied by —, should be established.

2. Please clarify as to whether other individual impurities are referred to either known or unknown impurities.

3. The regulatory specification for drug substance indicates that the acceptance criteria for — — and other individual impurities are —. Please justify this criteria.

4. Please provide validation data for GC method for — , in the drug substance , —) with a representative chromatogram. The validation data should include the — — , in the method.

5. The results of — tests for — and — testing on — — manufactured at — should be provided.

6. Please provide the numeric ranges for — — Refer to the Pre-NDA meeting minutes on 8-12-00 for —

7. The acceptance criteria for degradation products, —, should be tightened.

8. Please, justify the acceptance criteria for unknown individual impurities NMT —, and unknown total impurities, NMT —

9. Tighten the acceptance criteria for —

10. Please clarify the description of the secondary packaging components.

11. Please establish the acceptance criteria for [redacted] in the drug product specifications. The test method and justification of the acceptance criteria should also be included.

12. For the [redacted] system suitability parameters should be performed.

13. The storage statement in the package inserts, pouches, and cartons should state "Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 - 86°F).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee. Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Ira W. Klimberg, M.D.
Florida Foundation for Healthcare Research
3201 SW 34th Street
Ocala, Florida 34474

NOV 28 2001

Dear Dr. Klimberg:

Between October 2 and 5, 2001, Mr. R. Kevin Vogel, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #099009) of the investigational drug oxybutynin transdermal system, performed for Watson Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Vogel presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the observations that subjects 2105 and 2122 did not meet inclusion criteria due to lack of documentation of urinary void volume during two days of the 7-day baseline urinary diaries. We note that the Visit 3 case report forms for these subjects erroneously indicate that the subjects a) successfully completed the 7-day urinary diaries; and b) recorded in these diaries the volume voided during two consecutive days.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Vogel during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

FEI: 1000113813
Field Classification: Not stated
Headquarters Classification:
_____1) NAI
_X__ 2) VAI- no response required
_____3) VAI- response requested
_____4) OAI

If Headquarters classification is a different classification, explain why:

Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
_X_ failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-580 Doc.Rm. NDA #21-351
HFD-580 Review Div.Dir./Allen
HFD-580 MO/Gierhart
HFD-580 PM/Farinas
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File #10342
HFD-46 GCP Reviewer/Lewin
HFD-46 GCPI Br Chief/Martin
HFD-46 CSO/Ibarra-Pratt
HFR-SE250 DIB/Gallant
HFR-SE2585 Bimo Monitor/Torres
HFR-SE250 Field Investigator/Vogel

APPEARS THIS WAY
ON ORIGINAL

r/d: CL:11-21-01

reviewed:JM:11/27/01
f/t:ju:11/28/01

o:\cl\Klimberg N21351 Nov01 VAI.doc

Note to Rev. Div. M.O.

This routine clinical inspection was conducted in support of pending NDA #21-351 and focused on the conduct of protocol #099009. Our review of the establishment inspection report (EIR) reveals the following:

Twenty-three subjects were enrolled at this site; the number of subjects who completed the study is not discussed in the EIR. Records were reviewed for nine subjects. A Form FDA 483 was issued for two protocol violations: Subjects 2105 and 2122 were enrolled despite not meeting inclusion criteria; these subjects lacked documentation of urinary void volume during two days of the 7-day baseline urinary diaries. The Visit 3 case report forms for these subjects erroneously indicate that the subjects a) successfully completed the 7-day urinary diaries; and b) recorded in these diaries the volume voided during two consecutive days.

Data appear acceptable.

APPEARS THIS WAY
ON ORIGINAL

Status Meeting Minutes

Date: November 19, 2001 **Time**: 3:00 PM, EST **Location**: PKLN; 17B-43

NDA 21-351 **Drug:** oxybutynin transdermal system **Indication:** Overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Status

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sue-Jane Wang, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Young-Moon Choi, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D.- Pharmacokinetics Team Leader OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for this NDA.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for
3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor also submitted the tradename "Oxytrol" for OPDRA's consideration. Relevant meeting dates for this application are: November 10, 1999 for the End of Phase 2 meeting (IND 50,489); December 8, 2000 for the pre-NDA meeting; and June 13, 2001 for the filing meeting. The PDUFA goal date is February 26, 2002. The internal goal date for submission of the Action Package to the Division Director is February 12, 2001.

Discussion:
This status meeting was held electronically, with each reviewer submitting a status report via e-mail.
Clinical:

- Pediatric Development Plan:
  - letter was sent to sponsor on 10/23/01 approving partial waiver for under age 6 and denying issuing deferral at this time
  - the sponsor has submitted only a protocol outline for the proposed pediatric study; however, more details of a planned pediatric clinical trial are needed; the sponsor was asked to submit a complete protocol; the pediatric protocol has not been submitted to date
  - in addition, comments were sent on October 23, 2001 to the sponsor on their pediatric development plan; the sponsor called with 5 questions regarding the letter of October 31, 2001, and was asked to submit questions in a written submission, but none have arrived to date
- clinical inspection sites: Dr. Kroeger's site was acceptable; Dr. Antoci's and Dr. Klimberg's inspections are pending

- Safety Update:
  - the sponsor provided information on 73 patients who have been on oxybutynin patch for 12 months
  - the EOP2 meeting minutes (11/10/99) documented that the Division recommended that the sponsor submit data on use for 12 months on at least 50 patient; thus, the sponsor has met this criteria
- review ongoing

Toxicology:
- no issues at this time
- review ongoing

Clinical Pharmacology and Biopharmaceutics:
- review ongoing
- comments for the team will be forthcoming after discussion with team leader in December; time line is to finish the first draft of this NDA review on December 15, 2001 and the second draft a month later; OCPB briefing will be scheduled for end of January

Chemistry:
- review almost finished; additional review pending for recently submitted stability data

Statistics:
- review is ongoing
  - data from "099" has been reanalyzed regarding the normality assumption violation issue for Study 099009
  - review for Study "017" study is ongoing; this was an active controlled trial for oral oxybutynin designed to demonstrate non-inferiority
- timeline: review draft ready by mid-December
- preliminary review suggests that the statistical evidence is marginal and the effect size is small

Decisions made:
- reviews ongoing; every effort will be made to meet the internal goal dates

Action Items:
- Dr. Choi will provide comments to the team after discussion with the Clinical Pharmacology and Biopharmaceutics Team Leader
- Project Manager will call the sponsor to ascertain why the pediatric questions have not been submitted in writing (*in a December 2, 2001, telephone conference between Mr. David Campbell from Watson, and Ms. Farinas, Mr. Campbell indicated that questions will not be forthcoming; instead, the sponsor was to submit the pediatric protocol within one week*).

Drafted: Farinas/ 11.30.01
Concurrence: Rumble 11.30.01/Hirsch 12.14.01/Gierhart 11.30.01/Agarwal 11.30.01/Wang 11.30.01/ Choi Parekh
Finalized: Farinas/ 12.14.01

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/s/

Mark S. Hirsch
12/14/01 02:49:49 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 15 2001

Robert M. Kroeger, M.D.
Nebraska Clinical Research Center
8552 Cass Street
Omaha, Nebraska 68114-3907

Dear Dr. Kroeger:

Between October 16 and 18, 2001, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #099009) of the investigational drug transdermal oxybutinin, performed for Watson Laboratories, Inc.. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Montgomery during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

ESI

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

FEI: 3003414536
Field Classification: NAI
Headquarters Classification:
_X__ 1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted: None

cc:
HFA-224
HFD-580 Doc.Rm. NDA#21-351
HFD-580 Review Div.Dir./Allen
HFD-580 MO/Gierhart
HFD-580 PM/Farinas
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File #10491
HFD-46 GCP Reviewer/Lewin
HFD-46 GCP Br Chief/ Martin
HFD-46 CSO/Ibarra-Pratt
HFR-SW350 DIB/Woleske
HFR-SW350 Bimo Monitor/Montgomery

APPEARS THIS WAY
ON ORIGINAL

r/d: CL:11-14-01
reviewed:JM:11/14/01
f/t:jau:11/14/01

o:\cl**Kroeger N21351 Nov01 NAI.doc**

Note to Rev. Div. M.O.

This routine inspection was conducted in support of pending NDA #21-351 and focused on the conduct of protocol #099009. Eighteen subjects were enrolled at this site, 16 of whom completed the initial double-blind portion of the study. Eight subjects completed the subsequent open-label extension.

Records were reviewed for twelve subjects. No regulatory violations were noted; a Form FDA 483 was not issued. Our review of the establishment inspection report reveals that the study appears to have been conducted in compliance with FDA regulations.

Data appear acceptable.

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
Research Park
[illegible] Wakara Way
Salt Lake City, UT 84108

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Frank:

Reference is made to your correspondence dated September 4, 2001, requesting a partial waiver for pediatric studies for children under the age of six, and a deferral of pediatric studies until March 2003.

We have reviewed the information you have submitted and agree that a partial waiver is justified for Oxtyrol ™ oxybutynin transdermal system for the treatment of overactive bladder for the pediatric population.

Accordingly, a partial waiver for pediatric studies for children under the age of six for this application is granted under 21 CFR 314.55 at this time.

However, the Division will not grant your request for a deferral of pediatric studies at this time. Please submit your pediatric protocol for review with due diligence.

If you have questions, please contact Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

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

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ON ORIGINAL

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/s/

Daniel A. Shames
10/23/01 04:15:14 PM

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APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

To:	NDA 21-351
Through:	Mark Hirsch, MD Team Leader, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	October 12, 2001
Re:	BZ (Original Amendment) Oxytrol™ MO Review of Pediatric Development Plan/Request for Partial Waiver and Deferral of Pediatric Studies Correspondence Date: September 4, 2001 Date Received: September 5, 2001

Background:

During the EOP2 meeting on November 10, 1999, the sponsor was advised the following:

> sponsor should address the Pediatric Rule requirements for this drug for this indication ages 6 and older; Division recommends [redacted], sponsor can submit a request for deferral of Pediatric studies if unable to conduct studies at this time.

Pediatric studies were not discussed at the pre-NDA meeting held on December 8, 2000.

On April 26, 2001, Watson Laboratories, Inc submitted the Original NDA 21-351. It contained one paragraph regarding Pediatric Use (Volume 1, Section 1, on p. 30) in which the sponsor:

- Requested a deferral of Pediatric Studies until after NDA approval
- Proposed to conduct a study to address product use in children ages 6 and older [redacted]

On May 4, 2001, the sponsor was advised in a regulatory letter to submit their pediatric development plan within 120 days. In the same letter, the sponsor was told that the Division would review the plan and notify them of its adequacy within 120 days of receipt of their pediatric drug development plan.

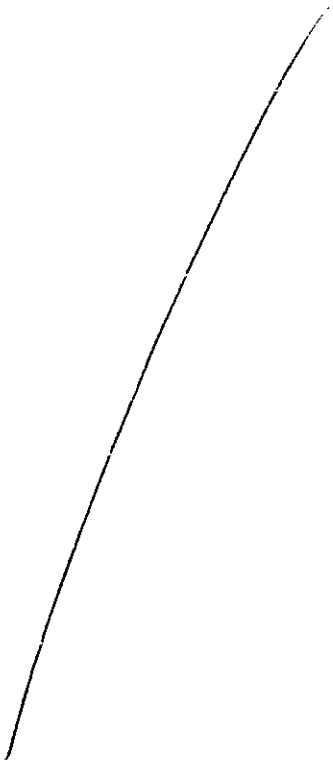
On June 13, 2001, the sponsor was notified that the information regarding pediatric studies submitted in Original NDA 21-351 was insufficient. They were told that to support their request for a deferral, they were to supply the certification for the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

Current submission:

In response, the sponsor now submits:

- Pediatric Development Plan

- Request for a partial waiver from pediatric studies for children under the age of six
- Request for a deferral submission of the final study report of the one planned pediatric study until . The anticipated start of the study is
- Protocol Synopsis entitled: '

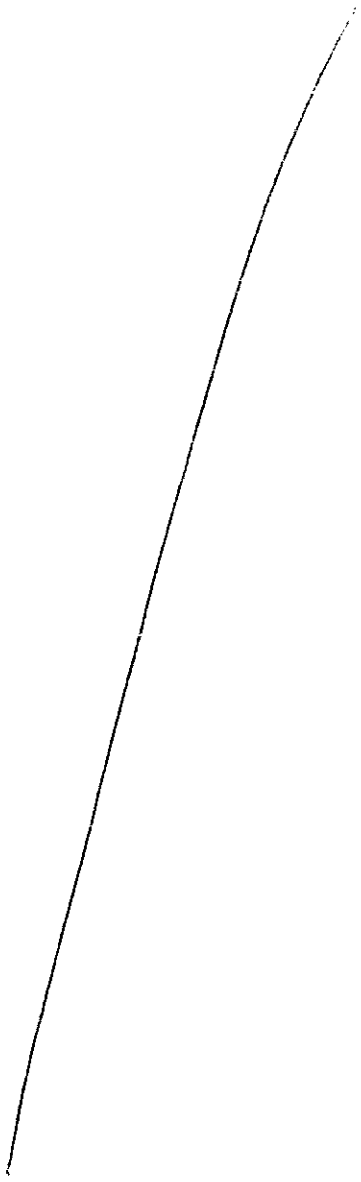


On October 11, 2001, statistical comments on this protocol were forwarded to the reviewer and are included in the following comments #3, 17, 18, and 19.

Reviewer's comment:

1) **Recommend granting the partial waiver for children aged less than 6 years. The sponsor has submitted adequate justification to support granting the partial waiver.**

2) **Recommend deferral not be granted until the pediatric protocol has been submitted and reviewed. The sponsor has not submitted evidence that the study will be conducted with due diligence and at the earliest possible time. Submitting the protocol will provide evidence that the study will be conducted with due diligence. Since the study is anticipated to be initiated ir —— , this request does not appear unreasonable to the reviewer.**
3) **Request sponsor submit the pediatric protocol for review with due diligence.**



Recommendation:

1) Grant the partial waiver for children aged less than 6 years.
2) Deferral not be granted pending review of pediatric protocol.
3) Comments #3-19 should be conveyed to the Sponsor.

cc: Original NDA 21-351
HFD-580: S. Allen, D. Shames, M. Hirsch, S. Wang, B. Gierhart, and E. Farinas

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/s/

Brenda Gierhart
10/14/01 03:07:21 PM
MEDICAL OFFICER

Mark S. Hirsch
10/15/01 07:50:49 AM
MEDICAL OFFICER

Status Meeting Minutes

Date: October 10, 2001 Time: 3:00-3:45 PM, EST Location: PKLN; 17B43

NDA 21-351 Drug: Oxytrol Indication: Overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. - Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, DNDC II @ DRUDP (HFD-580)
Sue-Jane Wang, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Young-Moon Choi, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D.- Pharmacokinetics Team Leader OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for this NDA.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for systems with oxybutynin delivery rates of [redacted] 3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor also submitted the tradename "Oxytrol" for OPDRA's consideration. Relevant meeting dates for this application are: November 10, 1999 for the End of Phase 2 meeting (IND 50,489); December 8, 2000 for the pre-NDA meeting; and June 13, 2001 for the filing meeting. The PDUFA goal date is February 26, 2002. The internal goal date for submission of the Action Package to the Division Director is February 12, 2002.

Discussion:
Clinical:

- Review: ongoing
- Issues:
  - pediatric studies need further sponsor clarification; [redacted]
  -

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- draft pediatric protocol synopsis was forwarded to the Clinical Pharmacology and Biopharmaceutics and Statistics reviewers for their feedback
- previous issues concerning removal of package insert prior to dispensing Oxytrol, and improper identification of the patch application sites were resolved; DDMAC and OPDRA indicated that the package insert is usually not given to patients; the sponsor submitted a revised patient package insert which clearly indicates the patch application sites

- Label: review started; comments are premature at this time
- Assessment: assessment is premature at this time

Toxicology:

- reviewer not present at the meeting
- reviewer indicated via e-mail dated October 11, 2001, that:
  - there are no approvability issues noted at this time
  - NDA review is on going
  - label review is premature at this time

Biopharmaceutics:

- Review: ongoing review of multiple PK studies (i.e., six studies); data appears to be acceptable regarding dissolution, although there are questions about time points; the sponsor will be contacted to provide additional time points data; first draft of review should be completed within a month
- Issues:
  - insufficient metabolism information provided; additional discussion with the sponsor is needed
  - lack of data on the 39-cm patch; preliminary review indicates that the data on the 13- and 26-cm patches are adequate; however, this needs to be reviewed in detail
  - wear studies indicate that a patch fell off in only one patient from Phase studies; there were also partial detachment data; this is a review issue
  - during review of the NDA, DRUDP will determine if the proposed pediatric PK study (50 subjects, aged 6 to 15, two centers) is acceptable, and if a partial waiver for pediatric studies can be granted; a population pharmacokinetic analysis will be adopted; the appropriateness of this plan will be reviewed when the full protocol is submitted
- Label: review is premature at this time
- Assessment: assessment is premature at this time

Chemistry:

- Review: review is on going
- Issues:
  - EES inspections on two sites are pending
  - data provided allows for ——— expiry data at this time; the sponsor will probably submit additional data that could extend the expiry to 24-months
  - drug-release deficiencies noted and communicated to the sponsor
  - linkage of the data between primary stability batches packaged in — pouches and the supporting batches packaged in peelable pouches was established
  - linkage of the dosing regimen to the trade name is not acceptable; the trade name should be identified separately from the dosing regimen
  - identification of oxybutynin as an "antispasmodic agent" in the package insert and the patient package insert versus "anticholinergic"; needs clarification from the clinical team
  - Microbiology review completed, indicating there are no problems with this application
- Label:
  - removal of the package insert from the carton prior to dispensing is acceptable

- Assessment: approval most likely

Statistics:

- Review: on going
- Issues:
  -
  - additional review is required because the sponsor's analysis plan has changed after the analysis of the clinical trial data
  - the medical team should identify the sections where the statistician's input is required
- Label: review is premature at this time
- Assessment: assessment is premature at this time

Decisions made:

- oxybutynin should be identified in the Oxytrol label using the same language as that of the Ditropan XL label

- the Clinical Pharmacology and Biopharmaceutics and Statistics reviewers will provide comments to the Medical Officer regarding the draft pediatric protocol
- the Statistics reviewer will provide comments to the Medical Officer via e-mail

Action Items:

- reviews will continue, and every effort will be made to meet the internal goal dates
- the sponsor will be asked to supply the information regarding the draft pediatric studies, time points data, and drug metabolism necessary for adequate review, in the near future

ADDENDUM:

**Comments from Clinical Pharmacology and Biopharmaceutics Reviewer
on NDA 21-351
During Status Team Meeting on 10/10/2001 (Wed)**

1. Regarding dissolution data:

The reviewing chemist provided individual release data from the all bio- and stability batches. This reviewer found that the sponsor provided dissolution data from — , per batch. The sponsor did not provided that the rationale for the proposed dissolution method and specification. It should be noted that the following data are normally needed to set up dissolution method and specification: (1) comparison of the dissolution profiles from 4 different media; (2) comparison of the dissolution profile in various paddle speed; (3) frequent enough sample collection for full description of dissolution profile.

This reviewer will closely review the appropriateness of the proposed dissolution method/specification using currently available data and discuss with team leader to decide whether additional data are needed or not.

2. Regarding the elimination pathway of Oxytrol:

It appeared that only 0.1 % of the dose is excreted in urine as parent and one active metabolite. It indicates that over 99 % of the dose is further metabolized to other metabolite(s). However, at this moment, this reviewer has not found the data or description for further elimination route. This reviewer will closely review on this.

3. Regarding the bioequivalency of 13 + 26 Cm^2 to 39 Cm^2 :

On the face and based on the filing memo of the former clinical pharmacology and biopharmaceutics reviewer, they seems like bioequivalent. However, it needs to be reviewed in detail.

4. Regarding pediatric study plan:

[redacted]

5. Regarding the adhesion (or wear) test:

The sponsor collected adhesion test data. From Phase I studies, one complete detachment has been observed. There were also partial detachment data. At this moment this reviewer are not able to make any conclusion for wear test. This reviewer will closely review on this point.

cc:
Drafted: Farinas/10.24.01
Concurrence: Rumble 10.24/Gierhart 10.15.01/Hirsch 10.31.01/Parekh/Agarwal10.24/Rhee 10.24/Wang 10.24.01/Choiy 10.31.01
Finalized: Farinas/ 11.09.01

MEETING MINUTES

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/s/

Mark S. Hirsch
11/13/01 10:57:28 AM

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Teleconference Minutes

Date: October 3, 2001 **Time:** 4:00 – 4:30 PM, EDT **Location:** PKLN; 17B45

NDA 21-351 **Drug:** Oxytrol (transdermal oxybutynin) **Indication:** overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Request for information

Meeting Chair: Rajiv Agarwal, Ph.D., Chemistry reviewer, Division of New Drug Chemistry II @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: David Campbell, Associate II, Regulatory Affairs, Watson Laboratories, Inc.

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Rajiv Agarwal, Ph.D. - Chemistry reviewer, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Dorothy A. Frank, M.S., R.A.C. – Executive Director, Regulatory Affairs
David Campbell – Associate II, Regulatory Affairs
Cherrie Petrie – Associate director, Regulatory Affairs

Meeting Objective: To request additional CMC clarification from the sponsor.

Background: Watson Laboratories, Inc., submitted NDA 21-351 for oxybutynin transdermal delivery system (TDS), [redacted] 3.9 mg/day, on April 26, 2001. Oxybutynin TDS is an adhesive matrix transdermal system intended to deliver oxybutynin at a constant rate over 96 hrs. This system is to be applied to the abdomen, buttocks or hip twice a week.

Discussion:

- the sponsor was asked to provide clarification for:
  - the discrepancy in the data of [redacted] presented on pages 288 and 289 of volume 1.2; it was noted that the number of [redacted] data (n=480) do not match the numbers of [redacted] data reported on page 289 of volume 1.2; the averages reported on page 289 in volume 1.2 do not match the average reported on page 290 of volume 1.2 (Table P 5.5-5)
  - additional real time stability data on primary stability batches
- the sponsor clarified that the release rates on [redacted] at [redacted] time points had been identified

APPEARS THIS WAY
ON ORIGINAL

Decisions made:

- the data, specifications and clarifications requested by DRUDP will be provided by the sponsor in a timely fashion

Action items:

- a copy of these minutes will be provided to the sponsor by DRUDP within 30 days of this teleconference

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Drafted: Farinas/10.9.01
Concurrence: Rumble 10.9.01/Agarwal 10.9.01
Finalized: 10.9.01

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/s/

Evelyn Farinas
10/9/01 04:26:40 PM
CSO

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Rajiv Agarwal
10/10/01 10:31:48 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

TELEFAX

TO: Davi Campbell
Watson Laboratories -
NDA 21-351 / Oxytrol -
FAX: 9-1801-583-8135
PHONE:

FROM:
Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

APPEARS THIS WAY
ON ORIGINAL

DATE: Sep 18/07

PAGES: 4 (Inclusive)

Dear David: Attached are the minutes of our Aug 30, teleconference.

Take care, Evelyn

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 30, 2001 **Time:** 1:00 – 1:30 PM, EDT **Location:** PKLN; 17B45

NDA 21-351 **Drug:** **Oxytrol** (transdermal oxybutynin) **Indication:** overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Request for information

Meeting Chair: Rajiv Agarwal, Ph.D., Chemistry reviewer, Division of New Drug Chemistry II @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: David Campbell

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Rajiv Agarwal, Ph.D. - Chemistry reviewer, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Dorothy A. Frank, M.S., R.A.C. – Executive Director, Regulatory Affairs
David Campbell – Associate II, Regulatory Affairs
Greg Arnold – Executive Director, Transdermal Development
Mamun Khan – Director, Analytical Services section
Jill Callahan – Manager Technical Services
Steve Sanders - Vice President, Proprietary Research and Development
Bill Good – Vice President, Transdermal Research and Development
Cherrie Petrie – Associate director, Regulatory Affairs

Meeting Objective: To request additional CMC data.

Background: Watson Laboratories, Inc., submitted NDA 21-351 for oxybutynin transdermal delivery system (TDS) — 3.9 mg/day, on April 26, 2001. Oxybutynin TDS is an adhesive matrix transdermal system intended to deliver oxybutynin at a constant rate over 96 hrs. This system is to be applied to the abdomen, buttocks or hip twice a week.

Discussion:

- the sponsor was asked to provide the following data to continue the review of this application:
  - the release rates on — at — time points for all the time intervals studied (i.e. — data for all pouches used)
  - the release rate on — at — for batch 0351/99Z162 at 30^0 should be submitted electronically
  - the results of " — test"; refer to the pre-NDA meeting minutes
  - the specifications for — in the drug product specifications

- data demonstrating that — is not observed when the systems are stored in "peelable pouch configuration"
- identification of the drug substance manufacturers and batch numbers of the drug substance, — , used to formulate the batches reported in the "stability data for peelable pouch configuration" (see page 386 of vol. 1.3
- to qualify the release liner manufactured at — for use in the drug product; USP tests (<87>, <88>, and <661>) should be provided and — of the drug product with — release liner should be placed on stability testing
- additional real time data to demonstrate that the product will be stable for the length of the requested expiry date in "peelable pouch configuration"
- the batch numbers of drug products manufactured using the — material, which were used in the clinical trials

- the sponsor was asked to provide clarification for:
  - the discrepancy in the data of ———— for batch 99Z137 at 30°; the average of these — at — does not match with the average reported on page 289 of vol 1.2 in specifications rationale, and with page 348 of vol. 1.3, stability data
  - the number of — batches and — that were used to manufacture the batches used in stability data for "peelable pouch configuration"
- the sponsor was asked to rectify the discrepancies (i.e., typographical errors) noted throughout the CMC section
- it was clarified that:
  - the description of the — test was covered in the Standard Operation Procedures
  - the differences regarding — pouches versus peelable pouches were in the degree of peelability, not the materials used
  - the information requested applies to the differences in peel strength between the peelable pouch and the — pouch
  - the peelable pouch, functionally, is an improvement for enhancement to aid the patient in opening the pouch; values are lower, but not critical to performance
  - — stability data is available for batch DP 133-01/C4; C4 is specific to the — liner
  - most likely, — materials were not used in clinical trials

Decisions made:

- the data, specifications and clarifications requested by DRUDP will be provided by the sponsor
- typographical errors will be corrected by the sponsor

Action Items:

- the sponsor will submit the information and clarifications requested within approximately two weeks of today's teleconference
- minutes will be sent to the sponsor in 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original IND
HFD-580/DivFile

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/s/

Evelyn Farinas
9/12/01 01:48:09 PM
CSO

Rajiv Agarwal
9/18/01 09:01:04 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

Status Meeting Minutes

Date: September 6, 2001 **Time**: 9:00-10:00 AM, EST **Location**: PKLN; 17B43

NDA 21-351 **Drug:** Oxytrol **Indication:** Overactive bladder

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sue-Jane Wang, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Young-Moon Choi, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D.- Pharmacokinetics Team Leader OCPB @ DRUDP (HFD-580)
Barbara Chong, Pharm.D. – Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of reviews for this NDA.

Background: NDA 21-351 for oxybutynin transdermal system was submitted on April 26, 2001. The sponsor is seeking approval for systems with oxybutynin delivery rates of [redacted] 3.9 mg/day for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The sponsor also submitted the tradename "Oxytrol" for OPDRA's consideration. Relevant meeting dates for this application are: November 10, 1999 for the End of Phase 2 meeting (IND 50,489); December 8, 2000 for the pre-NDA meeting; and June 13, 2001 for the filing meeting. The PDUFA goal date is February 26, 2002. The internal goal date for submission of the Action Package to the Division Director is February 12, 2001.

Discussion:
Clinical:

- Review:
  - ongoing review of Phase 3 Protocol 099-009, and of an additional open-phase, Phase 2 dose titration Protocol (096-017)
  - the sponsor submitted studies with three different sized patches, 13-, 26-, and 39 cm patch; it was clarified that the 26-cm patch delivers approximately 2.6 mg/day of oxybutynin and that the patches are to be applied twice a week

- the double-blind period of 099-009 for the 39-cm^2 arm utilized one 13-cm^2 and one 26-cm^2 patch; the open-label period of 099-009 utilized all three sizes if of patches (13-, 26-, and 39-cm^2)

- Issues:
  - the efficacy at the lower dose has not been consistently demonstrated
  - pediatric development plan has not been submitted; a facsimile was sent to the sponsor on June 14, 2001, providing clarification regarding the pediatric information required in the NDA submission; the sponsor was also reminded in this facsimile of the 120-day deadline for submission of pediatric plan or pediatric waiver requests (*the sponsor submitted a pediatric plan and a waiver request for studies in children under the age of six, dated September 4, 2001)*
  - it is unclear as to why the sponsor is instructing the pharmacist to remove the package insert before dispensing (*the Medical Officer indicated via e-mail that the package insert is intended for health care professionals only, and that the patient package insert only is being dispensed to the patients; this rationale is acceptable to the Medical Officer, but is being checked with OPDRA and DDMAC)*
- Label: review is premature at this time
- Assessment: assessment is premature at this time

Toxicology:
- Reviewer not present at the meeting

APPEARS THIS WAY ON ORIGINAL

Biopharmaceutics:
- Review: ongoing review of multiple PK studies (i.e., six studies)
- Issues:
  - no real data on the 39-cm patch; the data provided was on a combination use of the 26- and the 13-cm patches; it was noted that at the filing meeting it was agreed to accept the combination data as "fileable"; the equivalence between a 39-cm patch data and the combined data from the 13- and the 26-cm patches is a review issue
  - there is a potential for differences in adhesion among different body sites (*Medical Officer indicated via e-mail that the information about patch site application was included in Protocol 099009, located in Vol. 50, on page 68)*
  - metabolites need further review
  - individual data regarding dissolution specifications have not been submitted; the sponsor has been asked by the Chemistry reviewer to supply additional data for all batches at different time frames, and at several dissolution points; the sponsor may be contacted again to supply additional Biopharmaceutical data
  - wear data (adhesion) needs additional review; may recommend that label includes a statement indicating the lack of adhesion information regarding the 39-cm patch
- Label: review is premature at this time
- Assessment: assessment is premature at this time

Chemistry:
- Review: first draft of review has been completed
- Issues:
  - the main issue is the proposed expiry date; additional data has been requested from the sponsor to support ———h expiry; of concern is that the primary stability data was submitted for a pouch that is not the to-be-marketed pouch; some linkage can be made between the data from the — pouch and the peelable pouch
  - additional stability data is needed for the different release liners; it is critical to establish —, the sponsor was asked to conduct the necessary testing, since the DMF holder is not equipped to do such testing

- it was clarified that [redacted] is used to make one batch
- it was also clarified that [redacted] is used to make the three patch sizes
- EES inspections: two sites have been found adequate; the evaluation of two additional foreibn sites is pending
- Microbiology review noted deficiencies, which have been communicated to the sponsor
- the proposed tradename Oxytrol is acceptable

- Label: additional review is pending; some discrepancies have been noted, such as the need to remove the package insert from the carton prior to dispensing
- Assessment: premature at this time

Statistics:

- Review: ongoing review of Phase 2 study and Phase 3 pivotal studies: the additional information requested from the sponsor has been received
- Issues:
  - the statistical methodology used by the sponsor was modified, and requires additional review. the sponsor indicated that the data doesn't fit the normal distribution for the primary endpoint: proper evaluation of the efficacy results is a review issue
  - indexing of application is OK
  - it appears that the Phase 2 study is underpowered
  - the use of a smaller p value is a review issue
- Label: review is premature at this time
- Assessment: assessment is premature at this time

DDMAC:

- Review: is premature at this time

Decisions made:

- reviews will continue, and every effort will be made to meet the internal goal date
- each discipline will provide an individual discipline review, rather than a joint review

Action Items:

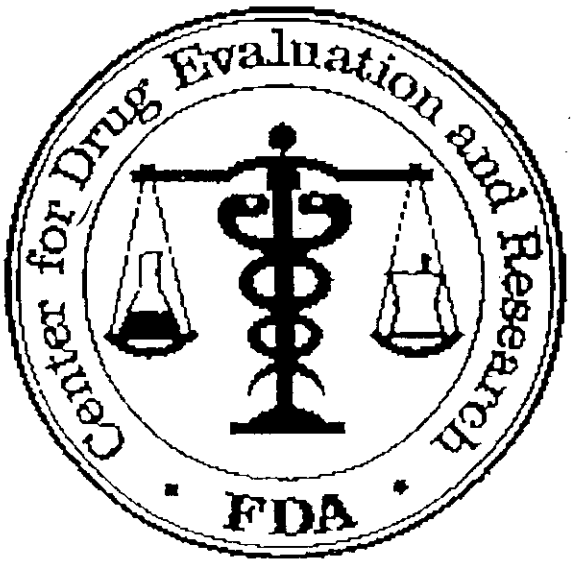
- Project Manager to contact the sponsor with the following requests:
  - state the date of the 120-day Safety Update submission (*submitted August 10, 2001; received August 13, 2001*)
  - state the date of pediatric plan submission (*submitted September 4, 2001; received September 5, 2001*)
  - state the date of wear data for the 13- and 26-cm patches submission (*sponsor contacted on September 14, 2001; data will be sent in the near future)*
  - clarify what advice is given to patients regarding swimming and bathing with the use of the Oxytrol patch (*sponsor contacted September 14, 2001; Medical Officer indicated via e-mail subsequent to the status meeting, that instructions for the patient are found in Vol. 1.1, page 65)*
  - submit Biopharmaceutics data electronically as desk copy for Dr. Choi (*sponsor contacted on September 14, 2001; electronic data will be sent to the Project Manager as a desk copy in the near future)*
  - submit a revised Patient Package Insert clearly showing the dotted areas in the sketch of the human figure where the patch should be applied *(sponsor notified September 14, 2001; sponsor indicated that the dotted areas appear in the electronic version, and noted that they were absent in the paper copy; sponsor will submit a revised PPI that includes dotted areas)*

- verify that the patch [redacted] as stated in Protocol 099009 *(sponsor notified September 14, 2001; sponsor indicated that the patch [redacted] and that this information is reflected in the Package Insert and in the Patient Package Insert)*
- Medical Officer to forward to the Team Leader a list of the contents of the 120-day Safety Update when available (*done on September 6, 2001)*
- Project Manager to attach the filing meeting minutes to this status meeting minutes (*see Attachment*)

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: August 31 / 2001



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TO: Watson Laboratories
David Campbell

Name:

Fax No: 9-1-801-533-8135

Phone No:

Location:

FROM: DRUDP

Name: Evelyn Farinas

Fax No: (301) 827-4267

Phone No: (301) 827-4260

Location: FDA, Division of Reproductive and Urologic Drug Products

Comments:

concurrence:

APPEARS THIS WAY
ON ORIGINAL

NDA - 21-351

August 31, 2001

Dear David:

Listed below are requests for additional information pertaining to Microbiology issues. It would be helpful if this information can be submitted together with the CMC data which was requested yesterday.

Take care,

Evelyn /S/

Microbiologist's List of Deficiencies and Comments:

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MEMORANDUM

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

Date: August 13, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-351

I have reviewed the financial disclosure information submitted by Watson Laboratories, Inc. in support of their NDA 21-351 for Oxytrol™ (oxybutynin transdermal system).

One pivotal Phase 3 study was conducted to assess the safety and efficacy of Oxytrol™ (oxybutynin transdermal system) for the treatment of patients with overactive bladder with symptoms of urge incontinence, urgency, and frequency. The study number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 099009/ Transdermal Oxybutynin in Patients with Urge Urinary Incontinence: A 12- Week, Multi-Center, randomized, Double-Blind, Placebo-Controlled, Study with a 12-Week Open-Label, Dose-Titration, Safety Period and a 28-Week Open-Label Safety Extension"	Begun after 2/2/1999	Appropriate documentation received, no financial disclosure submitted

Documents Reviewed:

- Financial Certification Information (Form FDA 3454) submitted April 26, 2001
- Response to Request for Information made June 13, 2001, (a table listing site, investigator, and number of patients) submitted June 27, 2001

Study 09009

Study 09009 started December 21, 1999 and completed July 26, 2000 (October 9, 2000, open-label extension). There were 199 principal and subinvestigators (investigators) at 40 sites (521 subjects) in this trial. Financial disclosure information was received for all investigators; none had any disclosable information.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of Trial 09009 in NDA 21-351.

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/s/

Jeanine Best
8/13/01 02:26:13 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 9, 2001

To: David Campbell	**From:** Evelyn R Farinas
Company: Watson	Division of Division of Reproductive and Urologic Drug Products
Fax number: 801-583-8135	**Fax number:** 301-827-4267
Phone number: 801-588-6375	**Phone number:** 301-827-4260

Subject: request for statistical data sets

Total no. of pages including cover: 2

Comments: Thanks for your help, Evelyn

Document to be mailed: ☐ YES ☑ NO

APPEARS THIS WAY ON ORIGINAL

Date: August 9, 2001

To: David Campbell, Regulatory Affairs

From: Evelyn Farinas, Project Manager

Re: Request for desk copies of statistical data

As stated in today's phone message, please submit the following as desk copies for the statistical:

- Datasets for ISS
- Datasets for study 096017
- Datasets for study 099009-DB
- Datasets for study 099009-OL
- ISS/ISE as Word files
- NDA reports (individual study reports and protocol)

Please send the desk copies of all of the above to:

Dr. Sue-Jane Wang
9B07 HFD-715
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

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/s/

Evelyn Farinas
8/9/01 04:02:21 PM
CSO

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3 Page(s) Withheld

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

√ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF TELECON

DATE: July 10, 2001

APPLICATION NUMBER: NDA 21-351. Oxybutynin transdermal system

BETWEEN:

Name:	David Campbell Regulatory Affairs
Phone:	801-583-8135 (facsimile)
Representing:	Watson Laboratories, Inc.

AND

Name:	Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Request for additional CMC information

BACKGROUND: NDA 21-351 was submitted on April 26, 2001. The additional CMC information is necessary for continued review of this application.

TELECONFERENCE SUMMARY:
The sponsor was asked (via facsimile) to provide the following information:

1. Please clarify how man — batches were used to manufacture the primary stability batches.

2. Please explain the differences in — manufacturing and clarify what process I used to manufacture the primary stability batches.

DECISIONS MADE:
The sponsor will provide the requested information as soon as possible.

Evelyn R. Farinas
Regulatory Project Manager

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/s/

Evelyn Farinas
7/18/01 11:32:44 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 14, 2001

To: David Campbell	**From:** Evelyn R. Farinas
Company: Watson Laboratories, Inc.	Division of Division of Reproductive and Urologic Drug Products
Fax number: 801-583-8135	**Fax number:** 301-827-4267
Phone number: 801-588-6200 x6375	**Phone number:** 301-827-4260
Subject: Clarification of pediatric submission	
Total no. of pages including cover: 2	

Comments:

Document to be mailed: ☐ YES ☑ NO

APPEARS THIS WAY ON ORIGINAL

NDA 21-351, Oxybutynin Transdermal System

Dear David:

To further clarify our conversation of June 13, 2001, regarding the pediatric information required in your NDA submission, I am forwarding you these comments. Please be aware that there is a deadline for your submission of the pediatric plan.

1. The information provided in NDA 21-351, Vol. 1, page 30, regarding Pediatric Studies is insufficient.

2. As I stated in my voice message, you must submit supporting information and documentation for your request for "deferral of Pediatric Studies until after NDA approval". Note that a deferral will be considered after you supply the certification for the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. A deferral is only granted until a certain point in time, so you need to submit a protocol synopsis and anticipated date of study completion.

3. Any request for a COMPLETE waiver of all pediatric studies with supporting information and documentation must be submitted by 60 days after date on the NDA 21-351 acknowledgment letter (which was 5/4/01). Or, as you state in page 30 of Vol. 1, you propose to study Oxytrol only in children ages 6 and older you must request a partial waiver (and provide justification) for neonates, infants, and children younger than age 6. An example of a justification would be if you provide documentation that the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group and is not likely to be used in a substantial number of patients in that age group. Other examples are listed in 21 CFR 314.55.

4. Please note that there is a 120-day deadline from the date of our acknowledgement letter of May 4, 2001, for submission of a request for a partial waiver and its justification, request for deferment (with protocol synopsis and date of study completion) and full pediatric development plan.

If you have questions, or if I may be of additional help, please call me at 301-827-4260. In my absence, ask to speak with Terri Rumble, Chief Project Management Staff, at the same telephone number.

Take care.

Evelyn

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/s/

Evelyn Farinas
6/14/01 09:15:25 AM
CSO

Evelyn Farinas
6/14/01 09:18:47 AM
CSO

Filing Meeting Minutes

Date: June 13, 2001 **Time**: 12:00-12:45 PM, EST **Location**: Parklawn; 17B43

NDA 21-351 **Drug:** oxybutynin transdermal system (TDS) **Indication**: [redacted]

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Filing

Meeting Chair: Daniel Shames, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ameta Parekh, Ph.D. – Clinical Pharmacology and Biopharmaceutics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB II; HFD 870) @ DRUDP (HFD-580)
D. J. Chatterjee, Ph.D. – Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB II (HFD 870) @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Michael Welch, Ph.D. – Statistics Team Leader
Barbara Chong, Pharm. D. – Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC)
Susan Molchan, M.D. – Medical Officer, Division of Scientific Investigations (DSI; HFD-46)
S. Wang, Ph.D. – Statistics Reviewer
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss fileability of NDA 21-351 (oxybutynin transdermal system).

Background: Watson Laboratories, Inc., submitted NDA 21-351 for oxybutynin transdermal delivery system (TDS), [redacted] 3.9 mg/day, on April 26, 2001. Oxybutynin TDS is an adhesive matrix transdermal system intended to deliver oxybutynin at a constant rate over 96 hrs. This system is to be applied to the abdomen, buttocks or hip twice a week. The pre-NDA meeting was held on December 8, 2000. In the present submission, the sponsor included efficacy data from only one pivotal Phase 3 study, on the 26 and 39 cm patches. The primary endpoint is [redacted], secondary endpoints are frequency and volume voided. An additional six-week trial was submitted in support of the pivotal study.

Discussion:

Clinical: fileable

- there are safety concerns regarding a single trial and supporting evidence being sufficient to support efficacy at the highest dose
- will contact sponsor to ascertain the information that will be submitted at the 120-day safety update
- the submission did not contain a pediatric plan; the sponsor may want to ask for a deferral of pediatric studies; the sponsor should be reminded to submit a pediatric plan within 120 days from the date of the June 4, 2001 acknowledgement letter; in addition, regarding the pediatric plan, the sponsor should be reminded to submit a request for a partial waiver and justification and request for deferral, with protocol synopsis and date of study completion

Biopharmaceutics: fileable

- most of the issues raised at the pre-NDA meeting have been addressed by the sponsor
- efficacy depends on the combined action of the parent drug and the metabolite
- the combined 13 and 26 cm patch appear to be dose proportional (i.e. additive) to the 39 cm patch
- TDS is not bioequivalent to the oral oxybutynin dosage form
- there are concerns about the adhesivity of the patches, particularly the 39 cm patch; studies were submitted for the 13 and 26 cm patches, but not for the largest size patch
- review of the NDA will determine if there is sufficient data on the 39 cm patch;
- the "to-be-marketed" formulation is the same as the "clinical-trials" formulation
- sponsor will be asked to submit electronic summaries of individual studies for ease of review

Chemistry: fileable

- major concern is that there are three drug substance manufacturers involved
- letter of authorization and Drug Master Files are available for review

Statistics: fileable

- of concern is that the formatting (i.e. the Index) is hard to follow
- open-label studies may be considered exploratory
- a more stringent criteria for P values is applied when there is only one pivotal study

DSI inspections:

- DRUDP should provide four sites for DSI inspections; sites will be selected based on recent site investigation history
- it was clarified that the primary endpoint is incontinence, i.e. a change from baseline in incontinence episodes; there are no co-primary endpoints
- the sponsor should be asked to submit a list of investigators sites, which should include the name of the investigator and the site's identification number, as well as the telephone number and the address for each site

Financial Disclosure:

- the sponsor will be contacted to send relevant information needed for financial disclosure assessment, i.e. a list of investigators sites, which should include the name of the investigator and the site's identification number, as well as the telephone number and the address for each site

General comments:

- the critical question is whether the data supports that the combination of the 13 and the 26 cm patches is bioequivalent to the 39 cm patch
- it may be useful to conduct a joint Biopharmaceutics and Clinical review, and issue joint recommendations

Action Items:

- Project Manager to contact the sponsor and ask the sponsor to:
  - indicate the additional information that is to be expected in the 120-safety update

- clarify if there are bridging bioequivalence studies between the (13 +26)cm and 39 cm patches; if these studies were done, the sponsor should identify where the data is located in the NDA submission
- provide electronic summaries in Word format of the individual studies to be reviewed by the Biopharmaceutics reviewer
- provide pediatric plan, as stated in the Pediatric Rule; refer the sponsor also to the acknowledgement letter *(pediatric plan located in Volume 1.1, page 30, requesting deferral of pediatric studies)*
- provide a list of the investigators, number of patients per site, and the address, telephone number, identification number for each site *(list submitted; information provided to Ms. Best for financial disclosure assessment; request for DSI inspection submitted to DSI first half of July)*

Minutes Preparer

Concurrence, Chair

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

cc:
IND Arch:
HFD-580/DivFile

HFD-580/ Allen/Shames/
drafted: Farinas, July 17, 2001
concurrence: Rumble 8.14/Shames 7.18/Hirsch 7.25/Gierhart 7.19/Parekh/Chatterjee/Rhee 7.24/Agarwal 7.27.01 Jordan/Chong/Welch 7.18.01/Wang/Molchan/
final: Farinas, 8.14.01

MEETING MINUTES

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/s/

Daniel A. Shames
3/17/01 04:37:27 PM

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ON ORIGINAL

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ON ORIGINAL

Teleconference Minutes

Date: May 15, 2001 **Time:** 3:30-3:45 PM, EDT **Location:** Parklawn; 17B-45

NDA 21-351 **Drug:** oxybutynin transdermal system **Indication:** incontinence

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Information request

Meeting Chair: Rajiv Agarwal, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: David Campbell, Associate II, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Rajiv Agarwal, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Steve Sanders - Vice President, Proprietary Research and Development
Bill Good – Vice President, Development
Greg Arnold – Executive Director, Transdermal Development
Mamum Khan – Director, Analytical Services
Tom Eckstein – Director Project Planning
Cherri Petrie – Manager, Regulatory Affairs
Jill Callahan – Manager, Technical Services
David Campbell – Associate II, Regulatory Affairs

Meeting Objective: To request additional CMC information from the sponsor.

Discussion:

- the sponsor was asked to submit the following information.
  - names of manufacturing, testing (release and stability), and packaging sites of the drug product if different from what is listed on page 3 of vol. 1.1
  - clarify which of the Watson facilities will be performing the testing on the drug substance
  - suppliers' Certificate of Analysis of drug substance batches used in the commercial batches; if the drug product manufacturer has performed the testing, submit the adopted acceptance and tests methods
  - batch numbers and drug substance manufacturer's name in the table where a summary of different clinical formulations are reported (see page 85, vol. 1.2)
  - batch number and names of the drug substance manufacturers used in the manufacturing of the primary stability batches and other supporting batches reported in the stability section
  - the chemistry, manufacturing and control information on the pouching material
  - relevant CFR reference to raw materials used in each pouching material
  - microbiological specifications for the drug product (see pages 278-281, vol. 1.2); microbiology section should be submitted for a microbiological consult review
  - specifications for [redacted] in the drug product should be provided
  - clarify if [redacted] was observed on release or stability testing of the patches
- the sponsor indicated that the information requested will be provided or if applicable, DRUDP will be notified of its location in the submission (volume and page number)

Decisions made:

- the sponsor will supply the CMC information

Action Items:

- the requested CMC information will be provided to the Division by the sponsor in a timely fashion
- Minutes will be sent in 30 days

Minutes Preparer **Concurrence, Chair**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original IND
HFD-580/DivFile
HFD-580/Allen/Shames/Agarwal/Rhee/Farinas/Rumble

drafted: erf/5.17.01
concurrence: Rumble 5.18.01/Agarwal 5.21.01/
final: erf/6.1.01

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Evelyn Farinas
6/1/01 02:47:48 PM
CSC

APPEARS THIS WAY
ON ORIGINAL

Rajiv Agarwal
6/1/01 02:54:26 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-351

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Frank:

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:	oxybutynin transdermal system, — 3.9 mg/day
Review Priority Classification:	Standard (S)
Date of Application:	April 26, 2001
Date of Receipt:	April 26, 2001
Our Reference Number:	NDA 21-351

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 25, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 26, 2002 and the secondary user fee goal date will be April 26, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Terri F. Rumble
5/4/01 04:28:06 PM

APPEARS THIS WAY
ON ORIGINAL

Pediatric Use

In accordance with 21 CFR 314.55 (b) and as recommended in the End of Phase II meeting with FDA on November 10, 1999, Watson Laboratories, Inc. requests a deferral of Pediatric Studies until after NDA approval. Watson is currently collecting additional data for the Oxybutynin Transdermal System in the adult population.

Dorothy A. Frank Date 04/24/01

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 12/04/00	**DUE DATE:** 05/18/01	**OPDRA CONSULT #:** 00-0327

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Evelyn Farinas
Project Manager
HFD-580

PRODUCT NAME:	**MANUFACTURER BY:**
Oxytrol (Oxybutynin Transdermal System) **IND:** 50,489	Watson Laboratories, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA has performed a review of the proposed proprietary name, Oxytrol, to determine the potential for confusion with marketed drug products and pending drug names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of the proposed proprietary name, Oxytrol.

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 05/01/01

IND: 50,489

NAME OF DRUG: Oxytrol (Oxybutynin Transdermal System)

IND HOLDER: Watson Laboratories, Inc

I. INTRODUCTION:

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for an assessment of the proposed proprietary drug name, Oxytrol.

PRODUCT INFORMATION
There were no container labels, carton labeling, or package insert available for review. Oxytrol is indicated for the [redacted]

[redacted] Oxytrol will be available as 39 cm^2 oxybutynin transdermal system, which delivers 3.9 mg daily. Oxytrol will be applied every 3 to 4 days.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike and/or look alike to Oxytrol to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA 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 proposed name, Oxytrol.

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] 2001 Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

A. EXPERT PANEL DISCUSSION

1. An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, Oxytrol. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and a representative 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.

   Seven products were identified in the Expert Panel Discussion that were thought to have potential for confusion with Oxytrol. These products are listed in the table, along with the dosage forms available and usual FDA-approved dosage.

Maxitrol	Dexamethasone/neomycin/polymyxin Opthalmic ointment: 3.5 g Opthalmic suspension: 5 mL	Ointment: Apply to affected eye (s) q 3 to 4 hours. Suspension: 1 or 2 drops into affected eye (s) BID to QID.	SA*
Emetrol (OTC)	Oral solution: each 5 mL contains dextrose 1.87 g, levulose 1.87 g, and phosphoric acid 21.5 mg.	Adults: 1-2 tablespoonfuls q 15 minutes until distress subsides.	SA*
Detrol Detrol LR	Tolterodine tablets: 1 mg and 2 mg 2 mg and 4 mg	1 to 2 mg BID 2 to 4 mg QD	SA*
Axotal	Butalbital and aspirin	**No longer marketed.**	SA*
Pitocin	**Oxytocin** injections: 10 units/mL	First, dilute 10 units in 1000 mL of IV fluid. Initial: 1-2 mU/min, increase 1-2 mU/min at 15-30 minute intervals. Maximum dose: 20 mU/min.	LA/SA*
Oxycel	oxidized cellulose **Pads:** 3" x 3", 8 ply **Pledgets:** 2" x 1"x 1" **Strips:** 18" x 2", 4 ply 5" x ½", 4 ply 36" x ½", 4 ply	Minimal amounts of an appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained.	LA/SA*
Oxistat	Oxiconazole 1%: Cream: 15, 30, 60 g Lotion: 30 mL	Apply to affected area QD and BID.	LA/SA*

*SA = Sound-alike
*LA = Look-alike

Of these products, Maxitrol, Emetrol, Detrol, Oxytocin, Oxycel, and Oxistat were considered to be most significant, because they sound and/or look like the proposed name, Oxytrol. Although Axotal sounds similar to the proposed name, it is no longer marketed in the United States.

2. DDMAC

DDMAC has no objection to the proposed name, Oxytrol.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

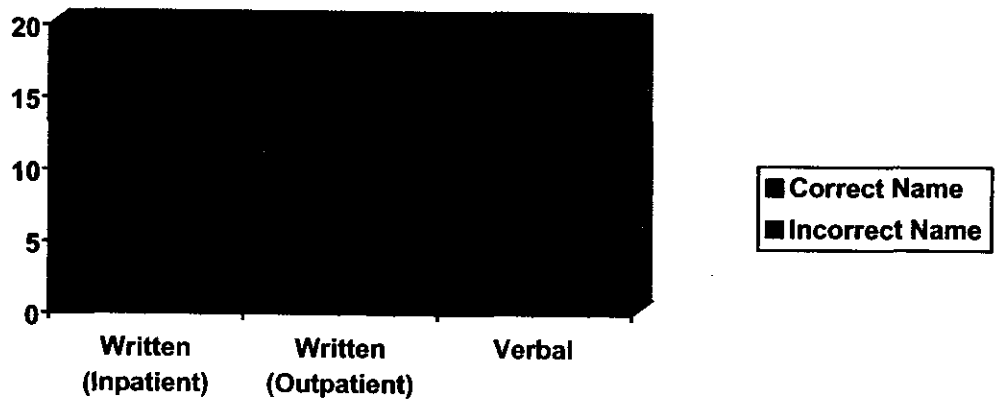
OPDRA conducted three studies involving 86 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Oxytrol and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Oxytrol (see below). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, the verbal order was 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
Outpatient Rx: Oxytrol Use 1 q 3 days as directed. #10	Verbal Rx: Oxytrol Use 1 q 3 days as directed. #10
Inpatient Rx: Oxytrol Use 1 q 3 days.	

2. Results:

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	28	20 (71%)	3 (15%)	17 (85%)
Written Outpatient	30	16 (53%)	13(81%)	3 (19%)
Verbal	28	13 (46%)	6 (46%)	7 (54%)
Totals	86	49 (57%)	22 (45%)	27 (55%)



Among the two written studies, 20 of 36 (56%) participants interpreted the name incorrectly. *One participant from the outpatient study interpreted the name as "Cytosol." Cytosol is no longer marketed in the United States.* The majority of the incorrect name interpretations were misspelled variations of "Oxytrol." Twelve participants interpreted the name as "*Oxytrel.*" Other incorrect interpretations were *Oxytol, Oxytial, Oxytel, and Oxytzel.*

Among the verbal prescription study participants for Oxytrol, 7 of 13 (54%) participants interpreted the name incorrectly. Most of the incorrect interpretations were phonetic variations of Oxytrol. Four participants interpreted the third letter "y" as an "i", "*Oxitrol.* Three participants interpreted the third letter "y" as an "a", *Oxatrol.*

C. SAFETY EVALUATOR RISK ASSESSMENT

We conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. Our study did not confirm confusion between *Oxytrol* and *Maxitrol, Emetrol, Detrol, oxytocin, Oxycel, or Oxistat.* One respondent from the inpatient study provided *Cytosol,* but this product is no longer marketed in the United States. Other misinterpretations did not overlap with any other currently approved drug names. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, Oxytrol. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size.

Maxitrol and Oxytrol are phonetically similar according to the expert panel. However, there is a low risk of confusion between Oxytrol and Maxitrol, because these two products share no commonalties other than similar names. Maxitrol and Oxytrol differ in dosage form, dose, strength, and dosing interval. Maxitrol is an ophthalmic agent that contains dexamethasone, neomycin, and polymyxin. It is available as opthalmic ointment (3.5g) and suspension (5 mL). Maxitrol opthalmic ointment is dosed every 3 to 4 hours, and Maxitrol opthalmic suspension is dosed twice to four times daily. It is unlikely that Maxitrol ophthalmic agent would ever be confused for Oxytrol transdermal system.

Emetrol is an over-the-counter oral solution that is used to treat nausea. It is dosed 1 to 2 tablespoonfuls every 15 minutes until distress resolves. The risk of confusion between Oxytrol and Emetrol is minimal, because both names are not phonetically very similar. Despite the same suffix, "trol," shared by both names, the prefixes, "Eme" and "Oxy" differ enough to distinguish one name from another. Moreover, Emetrol and Oxytrol belong to different pharmacological classes and are available in different dosage formulations. Lastly, it is unlikely that a patient expecting a transdermal system would get an OTC oral solution.

In regard to Detrol, there are similarities and differences in comparison to Oxytrol. Like, Oxytrol, Detrol (tolterodine) is also indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Unlike, Oxytrol transdermal system, Detrol is available as 1 mg and 2 mg tablets. Detrol is dosed 1 to 2 mg twice daily. Detrol is also available in long-acting formulation, Detrol LR. Detrol LR is available as 2 mg and 4 mg tablets and the recommended dose is 2 to 4 mg once daily. The risk of confusion between Oxytrol and Detrol is minimal given the differences in dose, dosage form, strength, and dosing frequency. Lastly, the prefixes, "Oxy" and "De" are different enough to distinguish one name from another.

Oxytocin is an approved established name for Pitocin. Oxytocin is commonly used for induction or stimulation of labor. Oxytocin was identified as a possible sound-alike and look-alike name, primarily due to its similar beginning, "Oxy." However, unlike the proposed drug, Oxytrol, Oxytocin is available as 10 units/mL injection and it must first be diluted in IV fluid. The initial dose should be no more than 1 to 2 mU/min (0.001 to 0.002 units/min). Furthermore, an infusion pump or other device must be used with oxytocin to accurately control the infusion flow. Given its restricted use and the method of administration, it is unlikely that these two drugs would ever be confused for one another and pose a significant safety risk.

Oxycel was also identified as a possible sound-alike and look-alike name, primarily due to its similar beginning, "Oxy." Oxycel contains oxidized cellulose and it is used adjunctively in surgical procedures to assist in the control of capillary, venous and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. Oxycel is available as pads, pledgets, and strips. Minimal amounts of an appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained. Given its restricted use, it is unlikely that these two drugs would ever be confused for one another and pose a significant safety risk. In addition, Oxycel would most likely be stored in surgical units and not in pharmacies, further decreasing the risk of medication errors.

There is a low risk of confusion between Oxytrol and Oxistat, because these two products share no commonalties other than similar names. These two drug products are available in different dosage forms, strengths, and dosing interval. Oxistat is an anti-fungal dermatological agent that contains the active ingredient, oxiconazole. It is used to treat tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), and tinea (pityriasis) versicolor in adults and children. Oxistat is available as 1% lotion and cream. Oxistat is applied once daily to twice daily. Oxytrol will be available as transdermal sytem that needs to be applied to skin every three to four days. Given the above differences in combination with the lack of convincing look-alike and sound-alike potential, it is unlikely that the proposed drug name would be confused with Oxistat.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Not supplied or reviewed.

IV. RECOMMENDATIONS:

OPDRA has no objection to the use of the proposed proprietary name, Oxytrol.

Labels and labeling for this product was not provided. OPDRA should review these when the NDA is submitted.

We would appreciate feedback of the final outcome of this consult. We would also be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Hye-Joo Kim at (301) 827-0925.

Hye-Joo Kim, Pharm.D.

Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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

/s/

Hye-Joo Kim
5/4/01 03:27:07 PM
PHARMACIST

Jerry Phillips
5/4/01 03:33:09 PM
DIRECTOR

Martin Himmel
5/7/01 10:36:41 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Watson Laboratories, Inc.
417 Wakara Way
Salt Lake City, Utah 84108

3. PRODUCT NAME

Oxybutynin Transdermal Delivery System

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THIS APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

CENTER FOR DRUG REC'D APR 26 2001 CDR EVALUATION AND RESEARCH

2. TELEPHONE NUMBER *(Include Area Code)*

(801) 588-6200

USER FEE I.D. NUMBER

4085

6. LICENSE NUMBER / NDA NUMBER

NO21351

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

CENTER FOR DRUG REC'D APR 27 2001 HFD-580 EVALUATION AND RESEARCH

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE: Dorothy A. Frank

TITLE: Director, Regulatory Affairs

DATE: 04/06/01

FORM FDA 3397 (5/98)

Created by Electronic Document Services/DSDHHS (301) 443-2454 EF

Meeting Minutes

Date: December 8, 2000 **Time**: 1:00-2:00 PM, EST **Location**: Parklawn; CR K

IND 50,489 **Drug:** transdermal oxybutynin — **Indication:** —

Sponsor: Watson Laboratories, Inc.

Type of Meeting: Pre-NDA

Meeting Chair: Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

External Lead: Dorothy Frank, Director, Regulatory Affairs, Watson Laboratories, Inc

FDA Attendees:
Susan Allen, M.D., M.P.H. - Director, DRUDP (HFD-580)
Daniel A. Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Medical Officer, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Shahla Farr, Ph.D.- Statistician, Division of Biometrics II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Dorothy Frank – Director, Regulatory Affairs, Watson Laboratories, Inc.
Steven W. Sanders, Pharm.D. – Vice President, Watson Laboratories, Inc.

Meeting Objective: To discuss NDA filing plans for oxybutynin transdermal system.

Background: In the November 14, 2000, (Serial Number 030) meeting package the sponsor submitted an outline of the NDA for Oxybutynin Transdermal Delivery System (Oxybutynin TDS), together with questions for the Division. The sponsor is planning to submit the NDA during the first half of 2001. The Oxybutynin TDS is an adhesive matrix transdermal system intended to deliver oxybutynin at a constant rate over 96 hours, and which is to be applied to the abdomen, buttocks or hip twice a week.

Discussion:

- DRUDP provided the following responses and comments to the sponsor's questions:

#1. Is the timing for filing this NDA acceptable with the Division? Is it acceptable to file this application under section 505(b)(1) of the Federal FD&C Act as amended?

- the timing for submitting this NDA appears to be acceptable, but additional comments as described in questions #10 and #11 were provided
- it is acceptable to submit this NDA under section 505(b)(1)

#2. Does the FDA agree that a hardcopy NDA is acceptable and only items 11 and 12 need be electronic?

- this is acceptable, but additional electronic data may be requested of the sponsor at a later time

#3. Are the overall structure and contents of the NDA Table of Contents acceptable to the Agency?

- this is acceptable

#4. Is the format and content of the CMC section adequate to support filing the NDA?

- this is acceptable
- the sponsor indicated that the "backing label" will be included in the NDA submission
- in the NDA submission the sponsor should:
  - provide justification for the specifications
  - include the specifications of — in the drug product
  - include — esting in the —
  - provide results of the — test, or provide the rationale for not doing this test
  - include mg patch data as well as percentage data in the stability data table
  - include batch records from biostudies or primary stability studies
  - provide data on how the three sources of drug substance will be qualified
- the sponsor should apply for a USAN name, and ask for an expedited review; the USAN name is necessary prior to approval
- the sponsor indicated that it would approach the — test as a one-time justification

#5. Does the FDA agree that the proposed structure and content of the Nonclinical Pharmacology and Toxicology section of the submission is adequate for filing?

- the proposal is acceptable
- the sponsor clarified that two studies would be included in the application, in addition to a reference section regarding oxybutynin published material

#6. Does the FDA agree that the proposed structure and content of the Human Pharmacokinetics and Bioavailability section of the submission is adequate for filing?

- the sponsor should:
  - address the issue of content of — over shelf-life (chemistry); if it decays over time, address the impact on drug exposure/efficacy
  - provide information on how delivery rate was calculated
  - provide effect of application site on drug exposure; indicate what was the application site in the clinical trial; indicate relative bioavailability to oral administration: ratios of parent drug (R and S) and metabolite (R and S)
  - provide data on development and validation of IVIVC
  - for *in-vitro* release specifications provide raw data from multiple batches

- address drug-drug interaction potential, if blood levels are expected to be different in oral versus transdermal system
- summarize dose-finding in the Clinical Pharmacology and Biopharmaceutics section
- population PK study, i.e., effect of age of patch; population age, race, gender, renally impaired, PK/PD, etc.
- provide supportive information for your statement "side effects are related to the metabolite levels"
- submit wear-study information
- if possible, DRUDP requests that the sponsor provide electronic submission as Word file, including narrative text, as review aids
- submit as much information as possible in terms of safety and efficacy to support comparability to the approved product

- the sponsor provided the following information:
  - the clinical trial formulation is not bioequivalent to the approved oral oxybutynin
  - the clinical trial formulation of the oxybutynin TDS is identical to the to-be-marketed formulation, cut to different sizes (13 and 26 cm^2) to maintain the blind; the dose proportionality study will provide information stating that the dose provided by the combined use of the 13 and 26 cm^2 sizes is equivalent to that of the 39 cm^2 size
  - the application site was restricted to the abdominal area only, although the site was rotated; data showed bioequivalence among buttocks, hips and abdomen
  - information will be included in the NDA submission showing that blood levels achieved with the transdermal formulation are comparable to those of the oral formulation
- DRUDP stated that the efficacy review of the NDA includes review of the clinical trial, and review of comparison studies showing that oxybutynin blood levels are comparable between the transdermal and the oral formulations

#7. Is the organization of study information in the Clinical Pharmacology section acceptable for the NDA? Is it acceptable to include "no studies conducted" in the clinical pharmacology section of Item 8?

- the sponsor will refer to appropriate published data in the Clinical Pharmacology section of their application

#8. Since no other uncontrolled studies were conducted, is the content of the Uncontrolled Clinical Studies section appropriate for the NDA submission?

- this is acceptable

#9. Is the content of the Other Studies section appropriate? Is it acceptable to present summaries of the Japanese investigations since completed reports of the trials will not be available at the anticipated time of NDA submission?

- this is acceptable; DRUDP recommends that the sponsor submit as much data from the studies described as possible

#10. Does the Division agree that the proposed content of the ISE will be adequate for filing?

- at this time, the proposed ISE appears to be adequate for filing; in the submission, the sponsor should address the following issues:
  - comparability of blood levels between the transdermal system and the oral formulation of oxybutynin
  - absence of a dose response

- indicate the numeric changes from baseline to endpoint and compare between treatment groups; it is premature to comment on the treatment effect at this time
- indicate if there is any treatment by center interaction or any particular subgroup that succeeded more than others

- DRUDP reminds the sponsor that it is risky to have only one pivotal trial if any significant issue surfaces during application review

#11. Is the proposed content of the ISS appropriate and sufficient to provide the Division with adequate data to assess the safety of the product?

- the extent of exposure described for the 39 cm^2 patch (109 patients for 11-12 weeks and 43 patients for 19-20 weeks) may not be adequate
- as stated at our End of Phase 2 meeting on November 10, 1999, DRUDP continues to recommend that the sponsor provide data on 300 patient for 6 months and 50 patients for one year (at the highest dose)

#12. Is the extent of exposure sufficient for the 39 cm^2 TDS, as described, with supporting information on the smaller system sizes?

- this is a review issue, not a fileability issue
- DRUDP recommends that the sponsor provide data on 50 patients at one year with the 39 cm^2 patch

- DRUDP recommends that the sponsor contact DRUDP prior to NDA submission to indicate if approval for one or both doses is requested

#13. Is the planned brief description of safety data from the Japanese studies appropriate for the ISS?

- DRUDP recommends that the sponsor provide as much information from these studies as possible

#14.Is the strategy for providing reviewer aids to the Division acceptable for the product labeling, ISS and ISE portions of the NDA?

- this is acceptable

#15. Is the planned content and timing of the Safety Update Report acceptable to the Division?

- safety update should be submitted four months after submission of the NDA
- DRUDP may request that a second safety update be provided at 90 to 120 days prior to action goal date, which is ten months after receipt of NDA submission

#16. Are the contents and electronic support described for the statistical section of the NDA sufficient for the statistical reviewer?

- this is acceptable; in addition, a hard copy of the statistical section is needed

#17. Does the Division agree with the strategy for submission of statistical analyses as described?

- the primary efficacy analyses and results of the study should be based on ITT population; ITT population should include all subjects randomized to the study; for subjects without any post baseline efficacy data, baseline value should be carried forward
- the statistical Analysis Plan (SAP) seems to be adequate; however, more detailed input would be a review issue and will be dealt with after the submission of the NDA

#18. Can the Division identify any additional analyses or supporting justification for the revision in the SAP that the agency will require during the review of the NDA?

- at this point in time, it is not necessary; if more information is needed, the sponsor will be notified

during the review process

- the sponsor indicated that:
  -
  -
  -
  - review aids and electronic files will be sent shortly after the NDA is submitted (i.e., between 10 and 45 days after submission)

Decisions reached:

- this NDA will be submitted under section 505(b)(1) of the FD&C Act
- the sponsor will submit a hardcopy of the NDA, with only items 11 and 12 as electronic submission
- the overall structure and contents of the NDA Table of Contents are acceptable
- the proposed format and content of the CMC section appears to be adequate
- the "backing label" will be included in the NDA submission
- the sponsor will apply for a USAN name
- the proposed structure and content of the Nonclinical Pharmacology and Toxicology section of the submission is adequate for submitting an NDA
- the content of the Uncontrolled Clinical Studies section is appropriate for the NDA submission
- the content of the Other Studies section is appropriate
- it is acceptable to present summaries of the Japanese investigations
- the proposed ISE appears to be adequate for NDA filing
- the strategy for providing reviewer aids to the Division is acceptable for the product labeling, ISS and ISE portions of the NDA
- a Safety Update will be submitted four months after filing date, followed by a second safety update at 90 to 120 days prior to action goal date
- the contents and electronic support described for the statistical section of the NDA is sufficient for the statistical reviewer
- a hard copy of the statistical section will be provided
- the sponsor will provide review aids and electronic files to the Division shortly after the NDA is submitted

Action Items:

- minutes will be provided to sponsor within 30 days

Minutes Preparer **Concurrence, Chair**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
IND Arch:
HFD-580/DivFile

HFD-580/ Allen/Shames/ Hirsch/Benson/Rhee/Mitra/Parekh/Farr
drafted: Farinas, 12.14.00
concurrence: Allen 01.08.00/Shames 01.03.01/Hirsch 12.28.00/Benson 12.14.00/Rhee 01.03.01/Mitra 01.02.01/Parekh 01.02.00/Farr 12.13.00/Rumble 12.18.00
final: Farinas, 01.08.01

MEETING MINUTES

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/s/

Susan Allen
7/13/01 03:26:37 PM
It should be noted that a hard copy version of these minutes was signe
d and previously sent to the sponsor on January 17, 2001.

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Meeting Minutes

Date: November 10, 1999 **Time:** 12:00-1:30 PM. EDT **Location:** Parklawn, Chesapeake Room

IND 50, 489 **Drug:** oxybutynin transdermal system **Indication:** overactive bladder

Sponsor: Theratech, Inc.

Type of Meeting: End of Phase 2

Meeting Chair: Lisa Rarick, MD – Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Meeting Recorder: Evelyn R. Farinas, RPh – Regulatory Project Manager

FDA Attendees:
Lisa Rarick, MD – Director, DRUDP (HFD-580)
Daniel Shames, MD – Medical Team Leader, DRUDP (HFD-580)
Norman Marks, MD – Medical Officer, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Terri Rumble, BSN – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Steven W. Sanders, Pharm D. – Vice President, Clinical Research and Project Planning
Dorothy A. Frank, M.S., R.A.C. – Director, Regulatory Affairs
Kim E. Caramelli, M.S. – Senior Clinical Scientist
Jacqueline Kalbach – Manager, Regulatory Affairs
Heather Thomas, Ph.D. – Biostatistician
Sidney Lyttle, MSc. - Biostatistician

Meeting Objective: To discuss proposed Phase 3 plan and pharmacokinetic studies.

Background: Oxybutynin free base is the active component in the oxybutynin transdermal system being developed by sponsor to treat [redacted]. Sponsor anticipates marketing this product in [redacted] to be applied twice weekly. In correspondence dated October 7, 1999 (Serial No. 15), sponsor is asking the Division for confirmation that sufficient data has been presented to initiate Phase 3 trials, and that the proposed Phase 3 plan is acceptable. The sponsor also wants Division's comments regarding the proposed human pharmacokinetic studies.

Discussion:

- sponsor presented overview of drug development program
- responses to the Clinical questions:
  1. a single efficacy and safety study may be sufficient to allow for NDA filability and review; robustness of the data submitted to support the claim of efficacy and safety will determine approval; there is risk in performing fewer rather than more trials to support safety and efficacy
  2. review of the final study reports will determine if the data from Phase 2 studies provide adequate supporting evidence for proceeding to Phase 3 trials for the oxybutynin transdermal system
  3. [redacted] are not acceptable to support product efficacy or labeling and promotional claims
  4. [redacted] may not be used as primary endpoints; global assessment measures are acceptable as secondary endpoints for exploratory analysis of relationship with objective clinically meaningful outcomes; [redacted]
  5. if the pharmacokinetics of the drug is shown to be similar to that of other approved formulations of oxybutynin, the data on 300 patients for six months would be satisfactory; however, the Division recommends data on use for 12 months on at least 50 patients given the chronic use of this class of drugs for this indication
  6. sponsor should address the Pediatric Rule requirements for this drug for this indication ages 6 and older; Division recommends that [redacted] sponsor can submit a request for deferral of Pediatric studies if unable to conduct studies at this time
- responses to the Biostatistics questions:
  - it is recommended that the study be performed with adequate blinding; it is acceptable to conduct a study in a partially blinded fashion provided that each active patch size is compared with its placebo patch size; placebo effect size may be a function of patch size
  - recommend comparison of active patch with placebo patch by size (i.e. large active patch vs. large placebo patch) and not pooling of information; may need larger sample size for multiple comparison adjustment
  - sponsor may consider increasing the number of subjects in the placebo group, or have subjects wear all 3 patches; if all 3 patches are worn together, irritation, partial lift, and fall-off issues should be addressed
  - randomization strategy will need to be revisited when the study design is finalized
  - recommend that sponsor define *a priori* the groups of centers to be used in the analysis; e.g., perhaps group centers by geographic region
  - protocol should explicitly specify the primary analysis to be used
  - recommend that sponsor explore treatment by center interaction
  - Division agrees that fixed-effect model is appropriate for analyzing effect of center
- comments on the Pharmacokinetics section:
  - The two PK protocols are acceptable; however, the sponsor is encouraged to measure R and S isomers of parent drug and active metabolite in the PK studies
  - Population PK/PD analysis should be performed using the sparse sampling data from the Phase 3 study
- response to the Pharmacology and Toxicology question:
  - data are sufficient to meet the requirements for a NDA

- responses to the Chemistry questions:
  - Division agrees that oxybutynin base is not a new molecular entity; it is considered a Type 2 chemistry designation
  - the proposal acceptable; however, sponsor reminded that drug product from the must be the same with will be reviewed with the NDA
  - s DMF need to be reviewed before determining if the drug substance, which were not used in the clinical studies, can be used in the commercial manufacture of the drug product

Decisions reached:

- a single efficacy and safety study may be sufficient to allow for NDA filability and review
- are not considered as primary endpoints
- or this indication are not considered primary endpoints
- data on 300 patients for six months is satisfactory provided that the pharmacokinetics of the drug is shown to be similar to that of other approved formulations of oxybutynin
- Pediatric Rule needs to be addressed for the drug development of this product
- it is recommended that the study be blinded
- randomization strategy for Phase 3 is acceptable
- Division agrees that fixed-effect model is appropriate
- data from the primary skin irritation study in rabbits and the guinea pig sensitization study plus a summary of the published literature on the preclinical safety of oxybutynin are sufficient to support the preclinical pharmacology and toxicology requirements for an NDA
- oxybutynin base is not a new molecular entity

Unresolved decisions:

- can not agree that data from Phase 2 studies provides adequate safety and efficacy data to support Phase 3 trials until final studies are reviewed
- manufacturer's information needs to be reviewed before determining if from each manufacturer is sufficient to support use of the material in the commercial manufacture of the drug product

Action Items:

- minutes will be provided to sponsor within 30 days

Minutes Preparer **Concurrence, Chair**

cc:
IND Arch: I 50489
HFD-580/DivFile

HFD-580/Rarick/
drafted: Farinas, 11.17.99
concurrence: Rarick 11.30.99/Shames 11.30.99/Marks 12.01.99/Kammerman 11.17.99/
Parekh/Jarugula 12.17.99/Rhee 11.30.99/Rumble 11.29.99
final: Farinas, December 17, 1999

MEETING MINUTES

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/s/

Lisa D. Rarick
6/12/01 10:22:56 AM

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-351	Efficacy Supplement Type SE-	Supplement Number: N-000-AZ
Drug: Oxytrol (oxybutynin transdermal system)	Applicant: Watson Laboratories, Inc.	
RPM: Jean King, M.S., R.D.	HFD-580	Phone # 301-827-4620
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	2S, 3S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	February 28, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA 3/26/02
• 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)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DMETS, 1/13/02; DDMAC, 4/6/02)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X [copy of Ditropan XL (tablets and syrup; extended release tablets) included]
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (11/10/1999)
• Pre-NDA meeting (indicate date)	X (12/8/2000)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (Team Leader, 2/21/03)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (2/21/03)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (see pages 47-66 of clinical review dated 2/21/03)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X (2/10/03)
❖ Statistical review(s) *(indicate date for each review)*	X (2/13/03)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (2/20/03)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (2/20/03)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X (2/20/03)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (see CMC review #1 dated 1/18/02)
• Review & FONSI *(indicate date of review)*	X (see CMC review #3 dated 2/20/03)
• Review & Environmental Impact Statement *(indicate date of each review)*	X (see CMC review #1 dated 1/18/02)
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (11/1/2001)
❖ Facilities inspection (provide EER report)	Date completed: 2/14/02 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharmacology/Toxicology	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (2/20/2002)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Jean R. King
2/24/03 03:57:20 PM
CSO

Jean R. King
2/24/03 04:00:04 PM
CSO

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-351 /SE ____ - ____

Drug Oxytrol (oxybutynin chloride transdermal patches) Applicant Watson Laboratories, Inc.

RPM Evelyn R. Farinas Phone 301-827-4245

x☐505(b)(1)
☐505(b)(2) Reference listed drug ____

☐Fast Track ☐Rolling Review Review priority: x☐ S ☐P

Pivotal IND(s) 50,489

Application classifications:
Chem Class 2S, 3S
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary February 26, 2002
Secondary March 26, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: x☐ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE x☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... NA
  Original proposed labeling (package insert, patient package insert) x
  Other labeling in class (most recent 3) or class labeling..... x
  Has DDMAC reviewed the labeling? ..... x☐ Yes (include review) ☐ No
  Immediate container and carton labels x
  Nomenclature review x

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is x☐ is not on the AIP.

  Exception for review (Center Director's memo)..... NA
  OC Clearance for approval..... NA

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter — NA

- Post-marketing Commitments — NA
  - Agency request for Phase 4 Commitments — NA
  - Copy of Applicant's commitments — NA

- Was Press Office notified of action (for approval action only)? — ☐ Yes x☐ No
  - Copy of Press Release or Talk Paper — NA

- Patent
  - Information [505(b)(1)] — X
  - Patent Certification [505(b)(2)] — NA
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] — NA

- Exclusivity Summary — X

- Debarment Statement — X

- Financial Disclosure
  - No disclosable information — X
  - Disclosable information – indicate where review is located —

- Correspondence/Memoranda/Faxes — X

- Minutes of Meetings — X
  - Date of EOP2 Meeting — 11/10/1999
  - Date of pre NDA Meeting — 12/8/2000
  - Date of pre-AP Safety Conference — NA

- Advisory Committee Meeting — NA
  - Date of Meeting — NA
  - Questions considered by the committee — NA
  - Minutes or 48-hour alert or pertinent section of transcript — NA

- Federal Register Notices, DESI documents — NA

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) — X

- Clinical review(s) and memoranda — X

- Safety Update review(s) — X

- Pediatric Information
  - x☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  - Pediatric Page —

☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda x
- Biopharmaceutical review(s) and memoranda x
- Abuse Liability review(s) .....
  Recommendation for scheduling ..... NA
- Microbiology (efficacy) review(s) and memoranda x
- DSI Audits X
  ☒Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda x
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... NA
- DMF review(s) X
- Environmental Assessment review/FONSI/Categorical exemption X
- Micro (validation of sterilization) review(s) and memoranda X
- Facilities Inspection (include EES report)
  Date completed _____ ..... ☒Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda x
- Memo from DSI regarding GLP inspection (if any) ..... NA
- Statistical review(s) of carcinogenicity studies ..... NA
- CAC/ECAC report ..... NA