

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-351

CHEMISTRY REVIEW(S)

NDA 21-351

Oxytrol
Oxybutynin transdermal system

Watson Laboratories Inc.

Rajiv Agarwal

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG
PRODUCTS**

Chemistry Review Data Sheet

1. NDA 21-351
2. REVIEW #: 3
3. REVIEW DATE: 20-FEB-2003
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	26-APR-2001
AMENDMENT	07-JUN-2001
AMENDMENT	13-JUL-2001
AMENDMENT	03-AUG-2001
AMENDMENT	09-AUG-2001
AMENDMENT	19-SEP-2001
AMENDMENT	25-OCT-2001
AMENDMENT	05-NOV-2001
AMENDMENT	08-JAN-2002
AMENDMENT	11-JAN-2002
AMENDMENT	14-FEB-2002
AMENDMENT	15-FEB-2002
AMENDMENT	27-FEB-2002
AMENDMENT	18-MAR-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AMENDMENT	29-AUG-2002
AMENDMENT	19-DEC-2002
AMENDMENT	05-FEB-2003
AMENDMENT	13-FEB-2003
AMENDMENT	14-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories Inc.

Address: 417 Wakara Way. Salt Lake City, Utah 84108

Representative: Ms. Dorothy Frank

Chemistry Review Data Sheet

Telephone: 801-588-6200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oxytrol
b) Non-Proprietary Name (USAN): Oxybutynin
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Treatment of patient with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

11. DOSAGE FORM: Transdermal System (39 cm²)

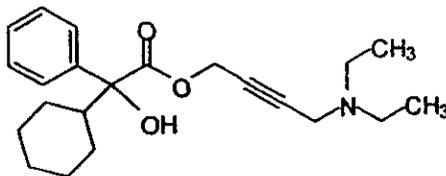
12. STRENGTH/POTENCY: 3.9 mg/day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]: SPOTS product – Form Completed Not a SPOTS product16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:Chemical Name:

4-(Diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate

Structural formula:



Molecular Formula: C₂₂H₃₁NO₃

Molecular weight: 357. —

17. RELATED/SUPPORTING DOCUMENTS:

- NDA Chemistry Review # 1 dated 18-JAN-2002
- NDA Chemistry Review # 2 dated 25-MAR-2002
- Chemistry IR letter for NDA 21-351 dated 06-DEC-2001
- T-con meeting minutes dated 12-FEB-2002 (regarding the clarification of deficiency # 3 in the IR letter and reminder to address the issues sent to the file holder of drug substance manufacturing site (DMF) —)
- EES inspection report: **Acceptable** 14-FEB-2002
- Trade Name: Approved by DMETS on 2-JAN-2003
- Chemistry Review # 2 of DMF — dated 14-FEB-2002
- Chemistry Review #2 of DMF — dated 26-FEB-2002
- Meeting minutes dated 12-DEC-2002

18. STATUS: Please refer to NDA Chemistry Review # 1 and # 2 dated 18-JAN-2002 and 25-MAR-2002, respectively, for more information.

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMETS	Acceptable	2-JAN-2003	Mr. Kevin Dermanoski



The Chemistry Review for NDA 21-351

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA may be approved from the CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Drug product (3.9 mg/day or 39 cm²) is an adhesive based transdermal system (patch). Each system consists of three layers (backing film, adhesive mix and protective release liner). Backing film (acetate), a film, is used to laminate the drug matrix on one side and printing on the other side. Adhesive matrix contains oxybutynin (36 mg), triacetin USP (a and (adhesive). Release liner is made of is supplied by

The drug product is packaged in a peelable pouch, which consists of and is considered to be adequate for protecting the systems during the shelf life from moisture, light, and microbiological contamination.

Applicant proposed 2-year expiry date and it is granted (see original NDA review # 2 dated 25-MAR-2002).

During the first cycle of review, the trade name consult was sent to OPDRA and an acceptable recommendation was received on 7-MAY-2001.

Since the trade name consult was provided over 12 months ago, the trade name **Oxytrol**, was again sent to the DMETS during the current review cycle. DMETS does not have any objections to the use of the proprietary name, Oxytrol (dated 2-JAN-2003).

Chemistry Review Data Sheet

Labels and interts were revised as suggested by this reviewer and deemed acceptable (see amendments dated -5-FEB-2003 and 13-FEB-2003).

Please refer to NDA Chemistry Review # 1 and # 2 dated 18-JAN-2002 and 25-MAR-2002, respectively, for more information.

Drug Substance:

Oxybutynin base, instead of previously approved Oxybutynin HCl, was used to formulate the drug product because of its _____

_____ different manufacturers' _____
_____ of the Oxybutynin are identified in the submission but the materials from _____ DMF # _____ and _____ DMF # _____ are used to formulate the drug product. Applicant withdrew the _____ site from the NDA.

Please refer to NDA Chemistry Review # 1 and # 2 dated 18-JAN-2002 and 25-MAR-2002, respectively, for more information.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose of Oxytrol is one 3.9 mg/day (39cm²) system applied twice weekly. Patient will remove the release liner and apply to a clean and smooth area of skin on the abdomen. Oxytrol delivers the medication slowly and continuously through the skin and into the bloodstream for 3 or 4 days.

C. Basis for Approvability or Not-Approval Recommendation

Based on the adequate CMC information (see NDA reviews dated 18-JAN-2002 and 25-MAR-2002) and satisfactory responses to the pouch, carton and package insert comments, this NDA may be approved from the CMC standpoint.

III. Administrative***A. Reviewer's Signature******B. Endorsement Block***

Rajiv Agarwal/Moo-Jhong Rhee/Jean King: Date: 20-FEB-2003

C. CC Block

HFD-580/Division File/NDA 21-351

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/s/

Rajiv Agarwal
2/20/03 01:38:14 PM
CHEMIST

Moo-Jhong Rhee
2/20/03 01:52:23 PM
CHEMIST
I concur



Chemistry Review Data Sheet

NDA 21-351

Oxytrol
Oxybutynin transdermal system

Watson Laboratories Inc.

Rajiv Agarwal

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-351
2. REVIEW #: 2
3. REVIEW DATE: 25-MAR-2002
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	26-APR-2001
AMENDMENT	07-JUN-2001
AMENDMENT	13-JUL-2001
AMENDMENT	03-AUG-2001
AMENDMENT	09-AUG-2001
AMENDMENT	19-SEP-2001
AMENDMENT	25-OCT-2001
AMENDMENT	05-NOV-2001
AMENDMENT	08-JAN-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
AMENDMENT	11-JAN-2002
AMENDMENT	14-FEB-2002
AMENDMENT	15-FEB-2002
AMENDMENT	27-FEB-2002
AMENDMENT	18-MAR-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories Inc.

Address: 417 Wakara Way, Salt Lake City, Utah 84108

Representative: Ms. Dorothy Frank

Telephone: 801-588-6200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Oxytrol
b) Non-Proprietary Name (USAN):	Oxybutynin
c) Code Name/# (ONDC only):	None
d) Chem. Type/Submission Priority (ONDC only):	

• Chem. Type: 3

Chemistry Review Data Sheet

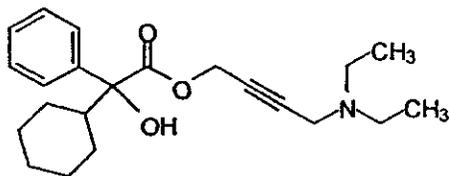
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable
10. PHARMACOL. CATEGORY: Treatment of patient with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
11. DOSAGE FORM: Transdermal System / → 39 cm²)
12. STRENGTH/POTENCY: — 3.9 mg/day
13. ROUTE OF ADMINISTRATION: — Transdermal
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:
Structural formula:

4-(Diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate



Molecular Formula: C₂₂H₃₁NO₃

Molecular weight: 357 —

17. RELATED/SUPPORTING DOCUMENTS:

- NDA Chemistry Review # 1 dated 18-JAN-2002

Chemistry Review Data Sheet

- Chemistry IR letter for NDA 21-351 dated 06-DEC-2001
- T-con meeting minutes dated 12-FEB-2002 (regarding the clarification of deficiency # 3 in the IR letter and reminder to address the issues sent to the file holder of drug substance manufacturing site (DMF
- EES inspection report: **Acceptable** 14-FEB-2002 (see the attached EER report) .
- Chemistry Review # 2 of DMF — dated 14-FEB-2002
- Chemistry Review #2 of DMF — dated 26-FEB-2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	14-FEB-2002	Ms. M. Garcia
Biopharm	Acceptable	22-MAR-2002	Dr. Yo ung Moon Choi
Methods Validation	The method validation package will be sent to and reviewed by FDA laboratories.		

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-351

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA can be approved from CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

Oxytrol : _____ 3.9 mg day (36 mg/system, 39 cm²), a drug product, is an adhesive based transdermal system (patch). _____ consists of three layers (backing film, adhesive mix and protective release liner). Backing film _____ acetate), a _____ film, is used to laminate the drug matrix on one side and printing on the other side. Adhesive matrix contains oxybutynin 36 mg), triacetin USP _____) and _____ (adhesive). Release liner is made of _____ is supplied by _____

The drug product is packaged in a peelable pouch, which consists of _____, and is considered to be adequate for protecting the systems during the shelf life from moisture, light, and microbiological contamination.

Applicant proposed 2-year expiry date and it is granted.

The trade name Oxytrol, was accepted by OPDRA.

Please refer to NDA Chemistry Review # 1 dated 18-JAN-2002 for more information.

Drug Substance:

Oxybutynin base, instead of previously approved Oxybutynin HCl, was used to formulate the drug product because of _____ different manufacturers (_____ of the Oxybutynin are identified in the submission but the materials from only _____ used to formulate the drug product.

The _____ manufacturing sites are in compliance to cGMP. The chemistry issues previously conveyed through the IR letter to _____ DMF # _____ and _____ DMF # _____ are satisfactorily resolved. However, due to the lack of _____

Chemistry Review Data Sheet

responses to the IR letter sent to — , DMF # — NDA sponsor withdrew the drug manufacturing facility.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose of Oxytrol is one 3.9 mg/day (39cm²) system applied twice weekly.

Patient will remove the release liner and apply to a clean and smooth area of skin on the abdomen. Oxytrol delivers the medication slowly and continuously through the skin and into the bloodstream for 3 or 4 days.

C. Basis for Approvability or Not-Approval Recommendation

Outstanding issues from Chemistry Review # 1 of NDA 21-351 and DMFs therein have been adequately resolved (see attached Chemistry Review notes).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Rajiv Agarwal/Moo-Jhong Rhee/Evelyn Farinas: Date 25-MAR-2002

C. CC Block

HFD-580/Division File/NDA 21-351

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/s/

Rajiv Agarwal
3/25/02 01:48:39 PM
CHEMIST

Moo-Jhong Rhee
3/25/02 04:58:57 PM
CHEMIST
I concur



Chemistry Review Data Sheet

NDA 21-351

Oxytrol

Oxybutynin transdermal system

Watson Laboratories Inc.

Rajiv Agarwal

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS



Chemistry Review Data Sheet

Chemistry Review Data Sheet

- 1. NDA 21-351
- 2. REVIEW #: 1
- 3. REVIEW DATE: 9-1-02
- 4. REVIEWER: Rajiv Agarwal
- 5. PREVIOUS DOCUMENTS: None

<u>Previous Documents</u>	<u>Document Date</u>
ORIGINAL	26-04-01
AMENDMENT	07-06-01
AMENDMENT	13-07-01
AMENDMENT	03-08-01
AMENDMENT	09-08-01
AMENDMENT	19-09-01
AMENDMENT	25-10-01
AMENDMENT	05-11-01
AMENDMENT	08-01-02

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Same as above	Same as above

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories Inc.
 Address: 417 Wakara Way, Salt Lake City, Utah 84108
 Representative: Ms. Dorothy Frank
 Telephone: 801-588-6200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oxytrol
- b) Non-Proprietary Name (USAN): Oxybutynin
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

Chemistry Review Data Sheet

Molecular weight: 357

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Deficient	12-10-01	Dr. Rajiv Agarwal, IR letter sent on 12-17-01
/	II	/	/	1	Deficient	12-10-01	Dr. Rajiv Agarwal, IR letter sent on 12-17-01
/	II	/	/	1	Deficient	12-10-01	Dr. Rajiv Agarwal, IR letter sent on 12-17-01
/	IV	/	/	3	Adequate	10-13-00	Dr Amit Mitra dated, 10-13-00
/	III	/	/	1	Adequate	12-12-01	Dr. Rajiv Agarwal, dated 12-12-01
/	IV	/	/	1	Adequate	12-12-01	Dr. Rajiv Agarwal, dated 12-12-01
/	III	/	/	3	Adequate	9-21-93	Dr. S. Basaran dated, 9-21-93
/	III	/	/	1	Adequate	12-12-01	Dr. Rajiv Agarwal, dated 12-12-01
/	III	/	/	1	Adequate	12-12-01	Dr. Rajiv Agarwal, dated 12-12-01

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Pending		
Pharm/Tox	Not applicable		
Biopharm	Pending		Dr. Choi Young
LNC	Not Applicable		
Methods Validation	Pending		
OPDRA	Acceptable	5/07/01	Hye-Joo Kim
EA	Categorical exclusion Granted		
Microbiology	Acceptable	10/11/01	Dr. Bryan S. Riley

The quality of the drug product is controlled by _____

_____ the acceptance criteria for degradation products however, seem to be too wide for _____ impurities and do not reflect the batch analysis or the stability of the drug product for 24 months. The acceptance criteria for these impurities should be **tightened to _____ and _____**, respectively, to reflect the manufacturing capability and stability of the product over time. Similarly, the provided acceptance criteria for **unknown individual and unknown total impurities should be also justified.**

The specifications of _____ and the _____ in the drug product are not provided. However, it is deemed acceptable because _____ are controlled during the manufacturing of _____ and provided data show that no significant _____ is observed during stability studies.

Microbiological testing is not included because applicant claims that _____ and microbiologist has agreed to their rationale.

In order to control the pouching of the drug product, the numeric ranges of the in-process controls such as _____

_____ are necessary for reproducibility of the future batches. Additionally, the acceptance criteria for _____ should be provided to further assure the quality of the product during shelf life.

The drug product is packaged in a peelable pouch, which consists of _____ (DMF _____), and is considered to be adequate for protecting the systems during the shelf life from moisture, light, and microbiological contamination during the shelf life.

The primary stability data (_____) is provided on the drug product packaged in _____, but the to-be-marketed product will be packaged in a "peelable pouch". The amount of stability data available from the product packaged in to-be marketed packaging "peelable pouch" is somewhat limited (up to _____ at long term and accelerated) but other supportive stability data from foil pouches (for the lowest strength) up to 2 years are available.

The clinical batches include a lowest strength (13 cm²) and both 13 and 26 cm² systems were used in the clinical trials to mimic the 39 cm² patch. The manufacturing process and the ratio of drug substance to excipients are same for all batches of different strengths and, therefore, the supporting stability data on the lowest strength were utilized for determining the expiry date. Similarly, the components of the _____ pouch and peelable pouch are the same, and therefore, there is no compatibility issue either. The different _____ process in peelable pouch creates only triangular flaps for an easy access to the patient.

Applicant proposed 2-year expiry date and it is granted.

The trade name **Oxytrol**, was accepted by OPDRA.

Drug Substance:

Oxybutynin base, instead of previously approved Oxybutynin HCl, was used to formulate the drug product because of its different manufacturers _____ (DMF _____), _____ (DMF _____), _____ (DMF _____) of the Oxybutynin are identified in the submission but the materials from _____ are used to

formulate the drug product. Drug substance from [redacted] was neither used in the clinical trials nor in the formulation of primary stability batches. However, a lowest strength (13 cm²) of drug product was manufactured by using the [redacted] material.

The quality of the oxybutynin manufactured at different sites is controlled by specification set by the individual manufacturer. Watson, the drug product manufacturer, also control the quality of the drug substance by performing in house testing with specifications [redacted]

[redacted], which are deemed satisfactory.

The results of test show that the drug substance produced at [redacted] sites are comparable except for the [redacted] in the drug substance manufactured at [redacted] manufacturing sites are using [redacted] utilizes [redacted] during the [redacted] synthesis. Therefore, it is necessary for the sponsor to establish a specification for the [redacted] for the drug substance supplied by [redacted]

The [redacted] manufacturing sites are in compliance to cGMP but the final recommendation from the Office of Compliance for [redacted] facility is still pending.

B. Description of How the Drug Product is Intended to be Used

The recommended [redacted] dose of Oxytrol is one 3.9 mg/day (39 cm²) system applied twice weekly.

Patient will remove the release liner and apply to a clean and smooth area of skin on the abdomen. Oxytrol delivers the medication slowly and continuously through the skin and into the bloodstream for 3 or 4 days.

Two years of expiry date is requested and granted. The storage condition is provided but according to the USP storage conditions, the storage statement in the package inserts, pouches, and cartons should be changed to "Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 – 86°F).

B. Basis for Approvability or Not-Approval Recommendation

This application is **approvable** from Chemistry, Manufacturing, and Control point of view. This recommendation is based upon several deficiencies found in the quality of the finished product. The sponsor needs to provide the justification and clarification for the inclusion of several impurities in the drug substance, and revise the acceptance criteria for degradation products. The sponsor also needs to provide justification for the inclusion of other impurities, which will reflect the actual manufacturing capability and stability characteristics of the drug product. Sponsor must provide the required USP tests (for safety and maintaining the quality) on the release liner, which protects the drug product. Furthermore, sponsor needs to establish the in process controls to monitor the manufacture of pouch. Sponsor also need to establish specifications to monitor [redacted] of the pouch to further assure the integrity of the pouch and therefore, the quality of the product during shelf life.

The system suitability of the analytical methods, which dictates the performance of the chromatographic method (HPLC) for meaningful interpretations of drug product specifications, needs to be provided. Lastly, the final recommendation from the Office of Compliance for [redacted] facility (Drug substance manufacturing site) is still pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Rajiv Agarwal/Date:
Moo-Jhong Rhee/Date
Evelyn Farinas/Date

C. CC Block

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Rajiv Agarwal
1/15/02 10:44:40 AM
CHEMIST

Moo-Jhong Rhee
1/18/02 04:36:04 PM
CHEMIST
I concur

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