CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

CHEMISTRY REVIEW(S)

NDA 22-204

Gelnique
(oxybutynin chloride) Gel
10%

Watson Laboratories, Inc.

Rajiv Agarwal

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

CMC REVIEW OF NDA 22-204
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 22-204

2. REVIEW #: 1

3. REVIEW DATE: 23-JAN-2009

4. REVIEWER: Rajiv Agarwal, Ph.D; Ph.D

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	26-MAR-2008
Amendment	29-JUL-2008
Amendment	11-SEP-2008
Amendment	31-OCT-2008
Amendment	22-JAN-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Watson Laboratories, Inc,.
Address:	577 Chipeta Way, Salt Lake City, Utah 84108
Representative:	Mr. Kevin Barber, Executive Director, Regulatory Affair
Telephone:	801-588-6324

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	GelNique
b) Non-Proprietary Name:	Oxybutynin Chloride
c) Code Name/# (ONDQA only):	N/A
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	3

CMC Review Data Sheet

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

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

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 100 mg/gram

13. ROUTE OF ADMINISTRATION: Topical

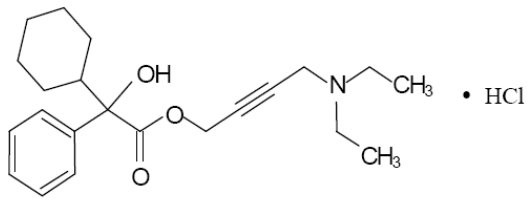
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

Chemical Name: 4-(Diethylamino)-2-butylnyl-α-phenylcyclohexaneglycolate hydrochloride
Molecular formula: $C_{22}H_{31}NO_3.HCl$
Molecular weight: 393.95



And enantiomers

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	21-OCT-2005	Dr. G. Sun
	II			3	Adequate	21-SEP-2006	Dr. R. Isern
	III			4	Adequate	2-DEC-2008	Information is provided in the NDA
	III			4	Adequate	2-DEC-2008	Information is provided in the NDA

[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 available11
7 – Other (explain under "Comments")

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,126	Active IND
EOF-2	67,126	6-SEP-2005
Pre-NDA	67,126	4-DEC-2007

CMC Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	23-JAN-2009	OC
Pharm/Tox	Acceptable	21-JAN-2009	Laurie Mcleod
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Acceptable	15-DEC-2008	Loretta Holmes
Microbiology	Acceptable	02-DEC-2008	Stephen Langille
EA	Categorical exclusion (see review)	02-DEC-2008	Rajiv Agarwal

The CMC Review for NDA 22-204

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance, oxybutynin chloride, is sourced from two different suppliers, (b) (4) and (b) (4) The Chemistry, Manufacturing, and Controls information pertinent to these drug substance, sourced from the (b) (4), is provided in DMF (b) (4) and (b) (4) respectively, and deemed adequate. For adequacy of oxybutynin chloride manufactured by (b) (4) and (b) (4) please refer to CMC reviews dated 21-OCT-2005 (by G. Sun) and 21-SEP-2006, (by R. Isern) respectively.

The applicant states that they perform testing as per the USP monograph, with the addition of an Appearance test. The applicant has observed two additional unknown impurities in the drug substance supplied by (b) (4) and the corresponding drug product. They have identified one as the (b) (4) and other to be an (b) (4) The applicant states that these impurities do not increase over time, and are controlled within limits set forth in the monograph. Since "any other single impurity" is controlled with a limit of NMT 0.1%, the levels of these new impurities are below the qualification limit, therefore are adequate. Additionally, structure/activity analyses predicted weak/equivocal carcinogenic effects for one of the isomers and low carcinogenic risk for the other. No biological data is however available, therefore, the established limit of 0.1% of 1 gram gel is equal to 1 µg, which

is below the 1.5 µg limit set for carcinogenic impurity. Pharmacology and Toxicologist reviewer accepts the limit.

(2) Drug Product

The drug product, a topical hydroalcoholic gel, is packaged in two different sachet configurations, made from (b) (4) materials. The Chemistry, Manufacturing, and Controls information pertinent to these packaging materials, sourced from the (b) (4) and (b) (4)), is provided in this NDA , and are deemed adequate.

The drug product is packaged in sachets constructed (b) (4) The NDA applicant has performed a number of suitability tests on both pouch stocks, including USP container Physicochemical testing, In-Vitro Biological Reactivity, and an Extractables/Leachables study. The (b) (4) pouching material leachable study found that of nine extractable components, only (b) (4) was present in the drug product at detectable levels. For the (b) (4) material, three leachables (b) (4) were detectable. The applicant has conducted toxicological evaluation of these leachables and states that the levels observed in the drug product are far below the acceptable daily intake. The applicant's evaluation of the limits for leachables for both pouch stocks is evaluated by the Pharmacology and Toxicology reviewer in collaboration with this reviewer and is deemed adequate.

For Impurities and Degradation Products, applicant has set the limit of (b) (4) at NMT (b) (4)% with the justification that it does not present a biological or safety impact since it is a metabolite that is pharmaceutically inactive and it is observed in the drug substance. Higher amounts (b) (4)%) of (b) (4) impurity was also present in Oxytrol, a transdermal system, also a Watson product, qualifies the amounts of (b) (4) impurity in this application. The applicant provides the specification for Total (b) (4) and (b) (4), which are deemed to be (b) (4)%, collectively these amounts are less than what was previously approved for Oxytrol, therefore, qualifies their amounts from the safety stand point.

The acceptance criteria for viscosity and in-vitro drug release for the drug product were tightened from its proposed range to reflect the manufacturing capabilities and stability characteristics. The applicant accepts the recommendation and amended the application with the requested information.

Microbial limits testing are conducted according to USP <61> methodology. The results of microbial limits testing conducted on nine batches of drug product were provided, which were tested for total aerobic microbial count, *E.coli*, *Salmonella* species, *Pseudomonas* and *Staphylococcus*, yeast and mold. The results of each test were within product specifications. All lots had (b) (4) of bacteria, (b) (4)

total yeast and mold count, and an absence of *E.coli* and *Salmenella*, *Pseudomonas* and *Staphylococcus.* The validation of the test methods and acceptance criteria are acceptable.

The applicant provides the stability data on 10 batches of drug product manufactured with (b) (4) sourced from two different manufacturers and filled into (b) (4) pouch stocks. The stability data indicates that the source of the drug substance, batch size and pouching material used in the manufacture of drug product stability batches does not influence the product quality over the proposed shelf life.

A 24-month of expiration dating period is granted for oxybutynin gel product packaged either (b) (4) sachet packaging at 20^0-25^0C (68^0-77^0F).

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

The contents of one sachet of Gelnique should be applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Application sites should be rotated. Application of Gelnique should not be made to the same site on consecutive days.

- A 24-month of expiration dating period is granted for the drug product packaged either (b) (4) sachets.

C. Basis for Approvability or Not-Approval Recommendation

- This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period.

- Labels have required information.

- All facilities have acceptable site recommendations (**refer attached-1**).

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Rajiv Agarwal, Ph.D; Ph.D

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D, Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

48 pp following this page withheld as (b)(4) CCI/TS.

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

/s/

Rajiv Agarwal
1/26/2009 08:07:49 AM
CHEMIST

Moo-Jhong Rhee
1/26/2009 08:58:53 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-204
Applicant:	Watson Laboratories
Stamp Date:	26-Mar-2008
PDUFA Date:	26-Jan-2009
Trademark:	Gelnique/ (b) (4)
Established Name:	Oxybutynin chloride topical gel
Dosage Form:	Gel
Route of Administration:	Transdermal
Indication:	Overactive Bladder
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	x	☐

Summary and Critical Issues:

A. Summary

Oxybutynin Chloride Topical Gel is a clear, smooth, odorless, and colorless hydroalcoholic gel containing 10% oxybutynin chloride in a 1 gram unit dose sachet composed of a (b) (4) It is referred to as a 10% or a 100 mg/g formulation throughout the application. Clinical studies were performed under IND 67,126, which was opened in April 2003.

B. Critical issues for review

Drug Substance

The drug substance, oxybutynin chloride, is sourced from two different suppliers, (b) (4) and (b) (4) Full information is provided in the referenced DMFs. Sponsor states that they perform testing as per the USP monograph, with the addition of an Appearance test. Sponsor has observed two additional unknown impurities in the drug substance supplied by (b) (4) and the corresponding drug product. They have identified one as the (b) (4) and believe the other to be an isomer of the (b) (4), but this has not been positively confirmed. Sponsor states that these impurities do not increase over time, and are controlled within limits set forth in the monograph. Since "any other single impurity" is controlled with a limit of NMT 0.1%, the levels of these new impurities are below the qualification limit. However, PharmTox should be notified of these impurities to determine if they are of toxicological concern for this route of administration and if they should be included as specified impurities in Specifications.

Drug Product

For Impurities and Degradation Products, sponsor has set the limit of (b) (4) at NMT (b) (4) % with the justification that it does not present a biological or safety impact since it is a metabolite that is pharmaceutically inactive and it is observed in the drug substance. Although this may be true, since it is a different route of administration, it is not know if there would be special toxicological concerns with dermal application. PharmTox should be made aware of the sponsor's justification. In addition, this degradation product has been seen to date at a maximum level of (b) (4) % and the (b) (4) % limit may not be justified. Sponsor may need to tighten the specification after a full review is made. Depending on the outcome of the limit for (b) (4), the specification for Total (b) (4) may also need to be tightened.

A specification for Total of All Impurities/Degradation Products should be added to the specification.

The specifications for Drug Release will require careful review to determine if the acceptance criteria are adequately set.

Sponsor plans to perform Microbial Limits testing on one batch/year. This will need to be evaluated by the Microbiology Reviewer and a consult will be sent.

The drug product is packaged in sachets constructed on one of (b) (4) Sponsor has performed a number of suitability tests on both pouch stocks, including USP container Physicochemical testing and In-Vitro Biological Reactivity, and an Extractables/Leachables study. The (b) (4) pouching material leachable study found that of nine extractable components, only (b) (4) was present in the drug product at detectable levels. For the (b) (4) material, three leachables (b) (4)) were detectable. Sponsor has conducted toxicological evaluation of these leachables and states that the levels observed in the drug product are far below the acceptable daily intake. Sponsor's evaluation of the limits for leachables for both pouch stocks should be evaluated by the PharmTox reviewer.

Sponsor states that stability data is provided on 10 batches of drug product manufactured with (b) (4) sourced from two different manufactureres and filled into (b) (4) pouch stocks. While the tables do list a total of 10 batches, it appears that 6 of the batches are only differentiated by the sachet used for packaging and the drug prodcut itself may be the same. Although this would make their stability package less extensive, the provided primary and supportive stability data still provides unique data on at least (b) (4) batches of drug product packaged in each sachet, so enough data will be available to make a decision on expiry. In addition, if the drug product bulk batches are the same, providing side-by-side comparison of the same batch in sachets composed of different materials will help to highlight any differences in stability due to packaging materials.

Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels.

The NDC number should be updated on the container labels. The NDC number should also be included on the Package Insert in the How Supplied section and should be included in the DLDE section of the SPL label

C. Comments for 74-Day Letter

Color mock-ups for the carton and immediate container labels, including any logos, should be provided in order to allow full review of these labels.

The NDC number should be updated on the container labels. The NDC number should also be included on the Package Insert in the How Supplied section and should be included in the DLDE section of the SPL label

D. Recommendation:

This NDA is fileable from a CMC perspective. There are several critical issues which need to be evaluated during the review as outlined above. There are two CMC comments to be included in the 74-day letter. A single reviewer, Rajiv Agarwal, Ph.D, Ph.D. has been assigned.

Donna F. Christner, Ph.D.

21 pp following this page withheld as (b)(4) CCI/TS.

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

/s/

Donna Christner
6/30/2008 10:34:49 AM
CHEMIST

Updated titles on filing checklist

Moo-Jhong Rhee
6/30/2008 10:39:04 AM
CHEMIST
Chief, Branch III