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RESEARCH**

APPLICATION NUMBER:

202211s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 202211
Supporting Documents:	S001
Applicant's letter date:	03/26/2010
CDER stamp date:	03/26/2010
Product:	Oxytrol for Women (Oxybutynin Transdermal System, 3.9mg/day)
Indication:	For the relief of overactive bladder symptoms for women ages of 18 and older.
Applicant:	Merck Consumer Care, Inc.
Review Division:	Division of Nonprescription Clinical Evaluation
Reviewer:	Cindy Xinguang Li, Ph.D.
Secondary Reviewer:	Paul Brown, Ph.D., ODE IV Associate Director for Pharmacology/Toxicology, OND
Division Director:	Andrea Leonard-Segal, M.D.
Project Manager:	Do, Phong, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA 202211) are owned by the applicant or are data for which the applicant has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that the applicant does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

1 Executive Summary

1.1 Introduction

This New Drug Application (NDA) was submitted by Merck Consumer Care, Inc. (MCC) for the drug product, Oxytrol for Women (Oxybutynin Transdermal System). The drug dosing regimen is a four day wear period over which the delivery will be approximately 3.9 mg/day. The product indication is for the relief of overactive bladder symptoms for women ages of 18 and older. This proposed indication presents a novel indication for over-the-counter (OTC) product.

The active ingredient of the drug product, oxybutynin, was first approved in the United States in July 1975 for oral use. Oxytrol, the transdermal formulation of oxybutynin, was developed by Watson Laboratories and was approved by FDA in 2003. The present NDA applicant MCC has obtained the right of reference of the data from Watson Laboratories and intends to change the marketing status of the same transdermal product from prescription (Rx) to OTC nonprescription. This Rx to OTC switch is a partial switch because MCC proposed that the OTC product only be used for women.

1.2 Brief Discussion of Nonclinical Findings

There are no nonclinical studies conducted or submitted for this NDA. The applicant refers to the data and the Agency's assessment of safety from nonclinical information submitted under NDA 21351 by Watson Laboratories.

1.3 Recommendations

1.3.1 Approvability

Based on the previous human use experience for oxybutynin compounds, the agency's previous review of the nonclinical information on the prescription product, as well as the lack of novel significant nonclinical toxicity findings identified during the current review, there is no impediment to approval of this NDA from a Pharmacology/Toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Based on the nonclinical data, the following information in the Rx label is recommended to be communicated in the OTC label: 1) Oxytrol should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during treatment are encouraged to contact their physician; 2) Administration sites should be rotated among abdomen, hip, or buttocks to avoid re-application to the same site within 7 days.

2 Drug Information

2.1 Drug

CAS Registry Numbers:
5633-20-5

Generic Names:
Oxybutynin

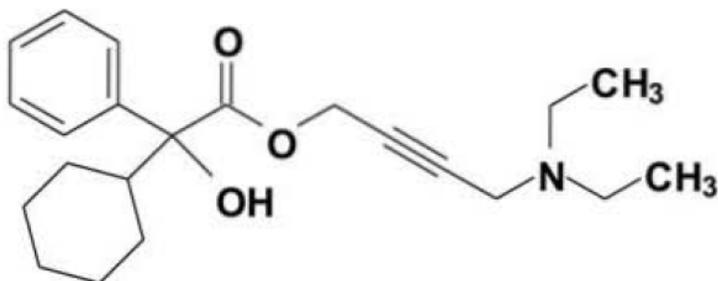
Trade Name:
Oxytrol for Women

Code Names:
None

Chemical Names:
4-diethylamino-2-butynyl-(±)-α-cyclohexyl-α-phenylglycolate

Molecular Formulae/Molecular Weights:
C₂₂H₃₁NO₃ / 357.5

Structure:



Pharmacologic Class:
Antispasmodic / Anticholinergic

2.2 Relevant INDs, NDAs, and DMFs

NDA 21351, Oxytrol (Oxybutynin Transdermal System), prescription product, Watson Laboratories, Inc.

2.3 Drug Formulation

The description of the product formulation is presented in the following table:

Table 1. Oxybutynin Transdermal System Composition

Description of Layers	Thickness (mil) ^e	Composition	
		mg/cm ²	mg/system
Backing Film	(b) (4)		(b) (4)
Adhesive Matrix			
Oxybutynin			
Triacetin.			
(b) (4) Acrylic Adhesive			
Release Liner			
TOTAL			
(b) (4)			
NA = Not Applicable			

Oxybutynin will be purchased from (b) (4) and the oxybutynin transdermal system will be manufactured at Watson Laboratories, in Salt Lake City, Utah.

2.4 Comments on Novel Excipients

None. Reference is made to NDA 21351 for Oxytrol. The excipients have been previously qualified and reviewed under NDA 21351.

2.5 Comments on Impurities/Degradants of Concern

None. Reference is made to NDA 21351 for Oxytrol. The impurities/degradants have been qualified and reviewed under NDA 21351.

2.6 Proposed Clinical Population and Dosing Regimen

The product is intended for the relief of overactive bladder symptoms for women age 18 and older. The dosing regimen is a four day wear period over which the delivery will be approximately 3.9 mg/day.

2.7 Regulatory Background

The first oxybutynin product, Ditropan oral tablet, was submitted by Janssen Pharms under NDA 17577. It was approved by FDA on July 16, 1975. Up to now there are three approved oxybutynin oral formulations including syrup at 5 mg/mL, tablet at 5 mg, and extended-release tablet at 5, 10, 15 mg. Oxytrol, the Oxybutynin Transdermal System,

was developed by Watson Pharmaceuticals and was approved by FDA on February 26, 2003 under NDA 21351. Gelnique which is oxybutynin in gel formulation was also developed by Watson Pharmaceuticals and was recently approved by FDA in 2009 under NDA 22204.

The present NDA submission is a partial Rx to OTC switch of Oxytrol (Oxybutynin Transdermal System) and is indicated for women only. This NDA refers to the data in NDA 21351 and the Agency's assessment of safety for that NDA. Watson Pharmaceuticals, the holder of NDA 21351, has granted MCC the right of reference to their data in the original NDA and all the subsequent supplements.

3 Studies Submitted

3.1 Studies Reviewed

None. No new nonclinical studies were conducted or submitted for the present NDA. The applicant refers to the data and the Agency's assessment of safety from nonclinical information submitted under NDA 21351 by Watson Laboratories.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Previous nonclinical reviews refer to Oxytrol (NDA 21351), Gelnique (NDA22204), Anturol (NDA202513), Ditropan (NDA17577, NDA18211), and Ditropan XL (NDA20897). A summary of toxicity studies with oxybutynin and oxybutynin transdermal product is presented in the following tables taken from the NDA submission:

Table 5.2.1-A Overview of Toxicity Studies for Oxybutynin TDS

Study	Species: Strain (No. per group)	Route and Dose / Concentration (mg/kg)	Result (Dose in mg/kg)	Reference
Acute Toxicity				
Single Dose	Rat: Sprague Dawley (10 per group)	Subcutaneous 0, 750, 3000, 12000, 48000	Minimum lethal dose-12000 to 48000. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Single Dose	Dog: Beagle (2 per group)	Subcutaneous 0, 125, 500, 2000	Minimum lethal dose- > 2000. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Single Dose	Dog: Beagle (2 per group)	Percutaneous 0, 0.625, 2, 5, 10 % body surface area	Minimum lethal dose- >1322 mg/m ² males, >1311 mg/m ² females. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Repeat Dose Toxicity				
4 weeks	Rat: Sprague Dawley (10 per group)	Subcutaneous 0, 24, 120, 600/day	Atoxic dose - < 24 mg/kg/day. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
4 weeks	Dog: Beagle (3-5 per group)	Subcutaneous 0, 12.5, 50, 200/day	5 of 5 animals died in 200 mg/kg/day group. No sex differences noted. Atoxic dose - <12.5 mg/kg/day.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
4 weeks	Dog: Beagle (3-5 per group)	Subcutaneous 0, 2, 10, 50/day	Atoxic dose - < 2 mg/kg/day 5 of 5 animals died in 50 mg/kg/day group. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
13 weeks	Rat: Sprague Dawley (10 per group)	Subcutaneous 0, 1.2, 9, 72/3-day	Atoxic dose - 9 mg/kg/3-day. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
13 weeks	Dog: Beagle (3 per group)	Subcutaneous 0, 1.2, 6, 30/3-day	Atoxic dose - 6 mg/kg/3-day. No sex differences noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Carcinogenicity Studies				
None				

Table 5.2.1-A Overview of Toxicity Studies for Oxybutynin TDS

Study	Species: Strain (No. per group)	Route and Dose / Concentration (mg/kg)	Result (Dose in mg/kg)	Reference
Special Toxicity				
Local Dermal Irritation	Rabbit: New Zealand White (6 total)	Topical (24 hour application)	Based on the average for the 24 and 72 hour readings, the primary dermal irritation index was calculated to be 0.8 (barely perceptible irritant) for the placebo patch and 1.9 (slight irritant) for the active drug patch.	Report RR95-0022 NDA 21-351, Volume 8 page 141
Dermal Sensitization	Guinea Pig: Hartley albino (42 total)	Topical (6 hour per application, 3 times a week for 3 weeks)	The oxybutynin and placebo patches did not produce delayed contact sensitization.	Report RR95-0023 NDA 21-351, Volume 8 page 157
Local Dermal Irritation (Draize method)	Rabbit: Japanese White (6 total)	Topical (24 hour application)	Very slight or distinctive erythema observed for oxybutynin and placebo preparations.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Local Dermal Irritation	Guinea pig: Hartley (12 total)	Topical (14 day application)	Very slight or distinctive erythema which was reversible was observed for oxybutynin preparation relative to placebo.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Dermal Phototoxicity (Morikawa method)	Guinea pig: Hartley (5 total)	Topical (24 hour application)	Following UV irradiation for 85 minutes, no phototoxicity was noted.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Dermal Sensitization	Guinea pig: Hartley (35 total-Adjuvant and Patch Test 35 total-Buehler method)	Topical	Approximately, one-half of these animals showed skin reactions such as erythema at the applied site following renewed exposure to oxybutynin indicating that oxybutynin had a skin sensitization effect.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Dermal Photosensitization (Adjuvant and strip method)	Guinea pig: Hartley (35 total)	Topical	Approximately, one-half of these animals showed skin reactions such as erythema at the applied site following renewed exposure to oxybutynin indicating that oxybutynin had a skin sensitization effect. Ultraviolet irradiation did not show a photosensitization effect	Report A-2-1-3 NDA 21-351, Volume 8 page 2

Table 5.2.1-A Overview of Toxicity Studies for Oxybutynin TDS

Study	Species: Strain (No. per group)	Route and Dose / Concentration (mg/kg)	Result (Dose in mg/kg)	Reference
Reproductive Toxicology				
Fertility and Primary Blastogenesis	Rat: Sprague Dawley (40 per group)	Subcutaneous daily to males and females 0,5,25,125 /day (daily administration to males for 4 weeks prior to mating)	The effect of oxybutynin on fertility was a decreased count of luteal bodies in the 25 mg/kg/day group. The number of implantations and live embryos were also decreased due to fewer luteal bodies, but there was no effect on the percentage of implantations or embryo mortality. Atoxic dose (parent)- <5 mg/kg/day Atoxic dose (fertility)- 5 mg/kg/day Atoxic dose (blastogenesis)- 125 mg/kg/day	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Embryo and Fetal Genesis	Rat: Sprague Dawley (18-20 per group)	Subcutaneous daily 0,1,5,25 /day during days 7 to 17 of gestation	There was no effect of oxybutynin on the maintenance of pregnancy of mother rats or embryo or fetal genesis. Atoxic dose (parent)- 1 mg/kg/day Atoxic dose (maintenance of pregnancy)- 25 mg/kg/day Atoxic dose (embryo and fetal genesis) - 25 mg/kg/day	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Embryo and Fetal Genesis	Rabbit: New Zealand White (16-20 per group)	Subcutaneous daily 0,0.2,0.3,0.4 /day during days 6 to 18 of gestation	There was no effect of oxybutynin on the maintenance of pregnancy of mother rabbits or embryo or fetal genesis in the 0.4 mg/kg/day group. Atoxic dose (parent)- 0.2 mg/kg/day Atoxic dose (maintenance of pregnancy)- 0.4 mg/kg/day Atoxic dose (embryo & fetal genesis)- 0.4 mg/kg/day	Report A-2-1-3 NDA 21-351, Volume 8 page 2

Table 5.2.1-A Overview of Toxicity Studies for Oxybutynin TDS

Study	Species: Strain (No. per group)	Route and Dose / Concentration (mg/kg)	Result (Dose in mg/kg)	Reference
Additional Studies				
Fertility (Segment 1 design)	Rat: Sprague-Dawley (24M, 24F per group)	Oral gavage 0,3,15,75 mg/kg/day	Mating performance and pregnancy rate were unaffected by treatment. The incidence of litters with one or more fetuses showing extra ribs was increased (significance unknown).	Edwards et.al., 1986 (8) NDA 21-351, Volume 9 page 37
Embryotoxicity (Segment 2 design)	Rat: Sprague-Dawley (36F per group)	Oral gavage 0,4,20,100 mg/kg/day	Reproductive performance was affected at 100 mg/kg/day and mean duration of gestation was extended. There were no clear effects at 4 or 20 mg/kg/day.	
Embryotoxicity (Segment 2 design)	Rabbit: New Zealand White (16F per group)	Oral gavage 0,3,12,48 mg/kg/day	No effect on embryo-fetal development was observed at the doses studied.	
Peri-Post Natal (Segment 3 design)	Rat: Sprague-Dawley (24F per group)	Oral gavage 0,4,20,50 mg/kg/day	No evidence of dystocia or extended gestation period was observed. Pup mortality was slightly increased and pup weight gain reduced at 50 mg/kg/day	

Table 5.2.1-A Overview of Toxicity Studies for Oxybutynin TDS

Study	Species: Strain (No. per group)	Route and Dose / Concentration (mg/kg)	Result (Dose in mg/kg)	Reference
Genotoxicity				
Bacterial Reverse Mutation Test	<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535 and TA1537 and <i>Escherichia coli</i> strain WP2uvrA	In vitro 2.5-80 µg/plate	Reversion was not observed in the presence or absence of metabolic activator.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Chromosomal Aberration Test	CHL cells	In vitro 12.5-400 µg/mL	Chromosome abnormality was not observed in the presence or absence of metabolic activator.	Report A-2-1-3 NDA 21-351, Volume 8 page 2
Micronuclear Test	Mouse	Subcutaneous 1250, 2500, 5000 mg/kg	Micronuclear increase was not observed.	Report A-2-1-3 NDA 21-351, Volume 8 page 2

4 Integrated Summary and Safety Evaluation

Oxybutynin is an antispasmodic, anticholinergic agent and is administered as a racemate (50:50) of R- and S-isomers. The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride. While the exact mechanism of action is unknown, oxybutynin is believed to produce a relaxant effect upon smooth muscle by antagonizing acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic receptor sites. Antimuscarinic activity of oxybutynin resides predominantly in its R-isomer. In animal models, oxybutynin administered intravenously, subcutaneously or intravesically has been demonstrated to have beneficial urodynamic effects, such as reducing maximum intravesical pressure, increasing bladder threshold volume and increasing bladder capacity. The active metabolite of oxybutynin, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies.

The oral formulation of oxybutynin was first approved in the United States in 1975. It is indicated for the relief of symptoms of urinary incontinence and urgency associated with

overactive bladder. The later-developed transdermal delivery system of oxybutynin provides advantages over oral formulations with regard to patient compliance, adverse effect profile and therapeutic efficacy. Oxytrol, Oxybutynin Transdermal System, was developed by Watson Laboratories and was approved by FDA in 2003. This product has a three layer matrix design and the three layers consist of a translucent backing film, an adhesive matrix, and an overlapped-tab release liner. The present NDA is a partial Rx to OTC switch of the same oxytrol product but is indicated for women population only.

The NDA applicant MCC has provided a nonclinical overview from Watson's original NDA submission 21351 and a review of relevant literature publications on oxybutynin. Overall there are no novel findings or unexplained toxicity observed:

General and special toxicity studies: The most often reported reactions from acute and chronic oral toxicological tests were extensions of the anticholinergic effects. In dermal irritation studies in rabbits, the oxybutynin patch was considered to be a slight irritant when applied acutely. Following fourteen-day, cumulative dermal irritation testing in guinea pigs, very slight to distinctive erythema was observed at the oxybutynin site from the beginning and increased until the 11th day, indicating a cumulative effect of skin irritation. This effect was reversible and the skin recovered during drug-free days. No dermal phototoxicity was observed following oxybutynin application to guinea pigs for 24 hours and ultraviolet irradiation. Likewise, the oxybutynin patches did not produce delayed contact sensitization.

Reproduction and developmental studies have been conducted to evaluate the fertility, reproductive and developmental performance of oxybutynin-treated rats and rabbits. In the rat, effects on reproductive performance included a slight increase in the incidence of fetal malformations, extended gestation period and impaired post-natal performance of offspring. However, these findings occurred at high doses associated with maternal toxicity. Oxybutynin did not exert an effect on reproductive processes in the rat at lower doses or on embryonic and fetal development in the rabbit. From the Oxytrol label:

Pregnancy Category B. There are no adequate and well-controlled studies using OXYTROL in pregnant women. OXYTROL should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during OXYTROL treatment are encouraged to contact their physician.

In a rat embryo/fetal developmental toxicity study, pregnant rats received up to 25 mg/kg subcutaneously of oxybutynin chloride. Maternal systemic exposure was estimated to be 50 times that of women treated at the maximum recommended human dose (MRHD) of 36 mg, based on body surface area. No embryo/fetal toxicity was observed in rats under the conditions of this study.

In a rabbit embryo/fetal developmental toxicity study, pregnant rabbits received oxybutynin chloride at up to 0.4 mg/kg subcutaneously. Maternal systemic exposure was estimated to be about equal that of women treated at the MRHD of 36 mg, based on body surface area. No embryo/fetal toxicity was observed in rabbits under the conditions of this study.

In mouse and hamster embryo/fetal development studies, no embryo/fetal toxicity was observed.

Mutagenicity of oxybutynin was tested by a bacterial reversion test, chromosomal aberration test using mammalian cells and a micronucleus test using mice. The results were all negative and no mutagenicity was seen. From the Oxytrol label:

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems. Reproduction studies with oxybutynin chloride in the mouse, rat,

Carcinogenicity was evaluated through oral route in rats and the study was reviewed under NDA17577 for oxybutynin tablet. From Oxytrol label:

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum exposure in humans taking an oral dose based on body surface area.

It was noted during the present NDA review that chronic dermal toxicity study in animals and dermal carcinogenicity bioassay were not conducted by the current or previous applicant. The following factors were considered: 1) Neither oxybutynin nor its main metabolite have structures that are similar to any of the compounds commonly associated with genotoxicity or carcinogenicity; 2) All genotoxicity studies of oxybutynin have been conducted and showed negative results; 3) Oral carcinogenicity findings were negative; 4) The administration sites of the product will be rotated among abdomen, hip, or buttocks; 5) The active ingredient in this product has been in clinical use for over 30 years and the transdermal use of oxytrol has also been almost a decade. The applicant reports no signal identified related to dermal carcinogenicity potential of oxybutynin or oxytrol. Therefore, the overall dermal carcinogenicity potential of the proposed product is considered to be low from the nonclinical perspective. This issue was discussed with the Division of Dermal and Dental Products at FDA. It was determined that based on the totality of the information, additional nonclinical studies for this patch product were not necessary at this time.

The excipients and impurities/degradants of the drug product have been qualified under NDA21351. There are no new pharmacology/ toxicology issues identified during this review.

Based on the previous human use experience of oxybutynin compounds, the agency's previous review of the nonclinical information on the prescription products, as well as the lack of novel significant toxicity findings during the current review, there is no impediment to approval from a Pharmacology/Toxicology perspective.

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/s/

XINGUANG LI
11/09/2012

PAUL C BROWN
11/09/2012

I concur with the recommendations.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202211 **Applicant:** Merck Consumer Care, Inc. **Stamp Date:** 03/26/2012

Drug Name: Oxytrol for Women (oxybutynin transdermal system, 3.9mg/day) **NDA/BLA Type:** 505(b)(1)

Background:

The present New Drug Application (NDA) is submitted by Merck Consumer Care, Inc. (MCC) for the product Oxytrol for Women (oxybutynin transdermal system). The indication is for the relief of overactive bladder symptoms for women ages of 18 and older. The dosing regimen is a four day wear period over which the delivery will be approximately 3.9 mg/day. This application is intended to change the marketing status of the product from prescription to over-the-counter nonprescription.

While the exact mechanism of action for oxybutynin is unknown, it is believed that it produces a relaxant effect upon smooth muscle by antagonizing acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic receptor sites. Oxybutynin was first approved for use in the United States in July 1975. There are currently eleven approved NDAs for three formulations (syrup-5 mg/mL, tablet-5 mg, extended-release tablet-5, 10, 15 mg). The oxybutynin transdermal system, which was developed by Watson Pharmaceuticals, Inc., has a three layer matrix design. The three layers consist of a translucent backing film, an adhesive matrix, and an overlapped-tab release liner that is removed prior to system application.

This NDA submission is a 505(b)(1) application where the sponsor is referring to the data and the Agency's assessment of safety from nonclinical information submitted under NDA 21351 by Watson Laboratories Inc. Watson Pharmaceuticals, Inc., the holder of NDA 21351 for the Rx Oxytrol transdermal system, has granted MCC the right of reference to the data in their NDA. The oxybutynin transdermal system will be manufactured at Watson Laboratories Inc., in Salt Lake City, Utah and Oxybutynin will be purchased from (b) (4)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

The descriptions of the product formulations are presented in the following tables:

Table 1. Oxybutynin Transdermal System Composition

Description of Layers	Thickness (mil) ^e	Composition	
		mg/cm ²	mg/system
Backing Film	(b) (4)		(b) (4)
Adhesive Matrix			
Oxybutynin			
Triacetin			
(b) (4) Acrylic Adhesive			
Release Liner			
TOTAL			
(b) (4)			
NA = Not Applicable			

On initial overview of the NDA application:

A dermal carcinogenicity study appears to be not available for this transdermal product. The sponsor may need to be contacted to address this issue.

There are no other pharmacology/ toxicology filing issues identified at this time.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on			This is a 505(b)(1) application where the sponsor is relying on data in NDA21351. A dermal carcinogenicity study was not conducted.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
	fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X*		*A dermal carcinogenicity study was not conducted with the product.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

At present, information identified that need to be forwarded in the 74-day letter is as follows:

A drug product applied to the skin with the potential to be used chronically is typically supported by chronic toxicity and carcinogenicity data by this route. Please address if you are aware of any chronic dermal toxicity studies or dermal carcinogenicity studies conducted with the oxybutynin product.

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/s/

XINGUANG LI
05/03/2012

PAUL C BROWN
05/03/2012