CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-103

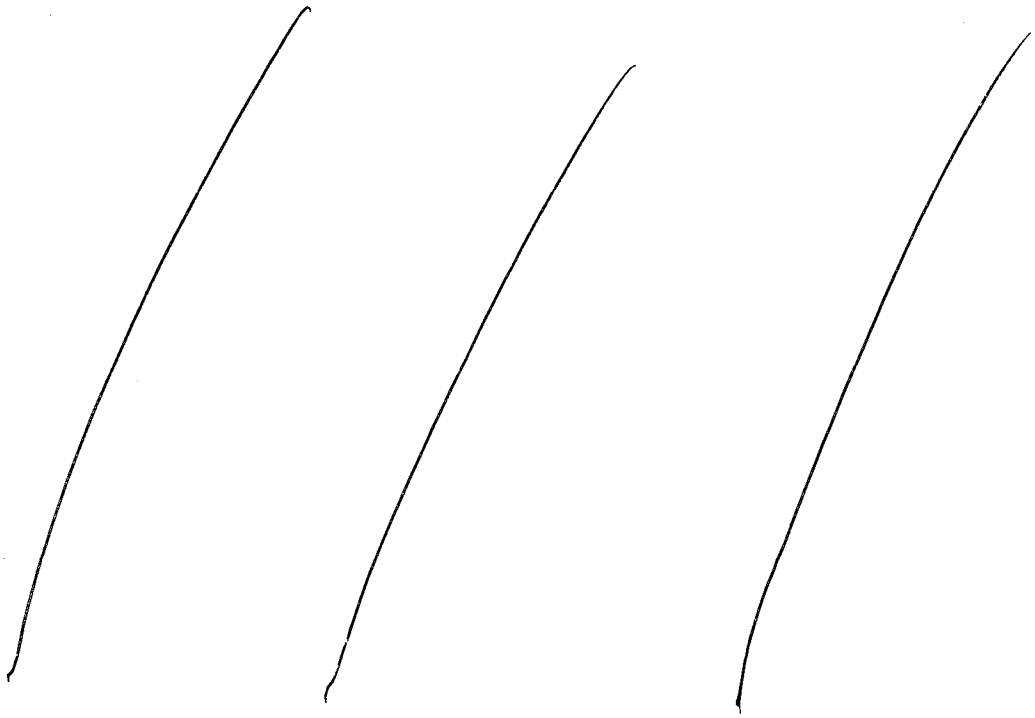
CHEMISTRY REVIEW(S)

Memorandum

To:	NDA 22-103
Through:	Moo-Jhong Rhee, Ph.D.
CC:	Donna F. Christner, Ph.D.
From:	Gene W. Holbert, Ph,D,
Date:	August 3, 2007
Re:	Carton and Container Labels

On 31-July, 2007 the following comments were submitted to the applicant concerning the carton and container labeling as recommended by DMETS:

In consultation with the Division of Medication Errors and Technical Support, we request the following revisions to container and carton label:



2 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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/s/

Gene Holbert
8/3/2007 01:59:54 PM
CHEMIST

Moo-Jhong Rhee
8/3/2007 02:14:00 PM
CHEMIST
Chief, Branch III

NDA 22-103

SANCTURA XR™

(trospium chloride extended release capsules)

Indevus Pharmaceuticals, Inc.

Division of Reproductive and Urologic Products

Gene W. Holbert, Ph.D.

Office of New Drug Quality Assessment
Division of Premarketing Assessment II

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-103

2. REVIEW #: 1

3. REVIEW DATE: 05-JUL-2007

4. REVIEWER: Gene W. Holbert, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-OCT-2006
Amendment (BC)	06-NOV-2006
Amendment (BC)	01-DEC-2006
Amendment (BC)	23-FEB-2007
Amendment (BC)	18-MAY-2007
Amendment (BL)	05-JUN-2007
Amendment (BC)	29-JUN-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Indevus Pharmaceuticals, Inc.
Address:	33 Hayden Avenue Lexington, MA 02421
Representative:	John Berryman Vice President, Regulatory Affairs
Telephone:	(781) 402-3451
Facsimile (FAX) Number:	(781) 863-2564

8. DRUG PRODUCT NAME/CODE/TYPE:

   a. Proprietary Name: Sanctura XR
   b. Non-Proprietary Name (USAN): trospium chloride
   c. Code Name/#: IP631
   d. Chem. Type/Submission Priority:
      - Chem. Type: 3
      - Submission Priority: S

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

10. PHARMACOLOGICAL CATEGORY: Antispasmodic: treatment of urinary incontinence

11. DOSAGE FORM: Capsules, extended release CODE: 610

12. STRENGTH/POTENCY: — 60 mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

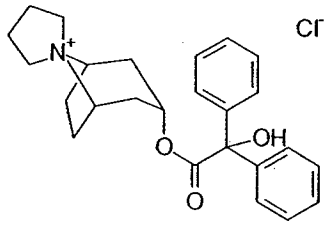
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

    __X__ Not a SPOTS product

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

    USAN/INN: Trospium chloride
    CAS: (1α,3β,5α)-3-[(Hydroxydiphenylacetyl)oxy]spiro[8-azoniabicyclo[3.2.1]-octane-8,1'-pyrrolidinium] chloride



Molecular Formula: $C_{25}H_{30}ClNO_3$ Molecular Weight: 427.97 CAS: 10405-02-4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Trospium chloride	1	Adequate	15-DEC-2006 G. Holbert	LOA 25-OCT-2005
	II		Trospium chloride	1	Adequate	22-JUN-2007 G. Holbert	LOA 29-JUL-2005
	III			3	Adequate	29-JUL-2003 J. Boal	LOA 27-SEP-2006
	III			3	Adequate	06-DEC-2004 R. Madurawe	LOA 19-SEP-2006
	III			3	Adequate	15-SEP-2000 D. Klein	LOA 20-SEP-2006
	III			3	Adequate	02-SEP-2003 Bing Wu	LOA 23-FEB-2007
	III			3	Adequate	30-MAY-2003 L. Roca	LOA 19-SEP-2006
	III			3	Adequate	06-DEC-2004 R. Madurawe	LOA 02-OCT-2006
	III			1	Adequate	07-DEC-2006 G. Holbert	LOA 19-SEP-2006
	III			1	Adequate	04-DEC-2006 G. Holbert	LOA 19-SEP-2006
	III			3	Adequate	12-JUL-2004 L-S Hsieh	LOA 02-OCT-2006
	IV			3	Adequate	01-NOV-2005 S. Pope	LOA 24-AUG-1006
	IV			3	Adequate	30-DEC-2002 G. Lunn	LOA 26-SEP-2006
	IV			3	Adequate	12-SEP-2001 Y. Pan	LOA 24-AUG-2006
[redacted]	IV	[redacted]	[redacted]	1	Adequate	18-APR-2004 G. Holbert	LOA 04-AUG-2005

[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")

[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
NDA	21-595	Sanctura® (trospium chloride) tablets, 20 mg
IND	71,305	Sanctura® (trospium chloride) tablets, 20 mg

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	16-JUL-2007	S. Ferguson
Pharm/Tox			
Biopharm	Acceptable	28-JUN-2007	S.K. Apparaju
DMETS	Sanctura XR acceptable not recommended	25-JUN-2007	Kimberly Culley-Pedersen
Methods Validation	N/A		
OPDRA			
EA	Categorical exclusion	15-JUN-2007	G.W. Holbert
Microbiology	Approval	11-APR-2007	B.S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 22-103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of this application is recommended from the CMC perspective pending receipt of acceptable final container/carton labeling.

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)

Sanctura XR™ (trospium chloride extended release capsules) are [redacted]. The capsules are designed to deliver trospium chloride more slowly than the approved immediate-release formulation (NDA 21-595, approved May 28, 2004), permitting once-a-day administration.

In addition to trospium chloride, Sanctura XR Capsules contain Sugar Spheres NF, Hydroxypropyl Methylcellulose USP, [redacted] Methacrylic Acid Copolymer [redacted] Triethyl Citrate NF, Talc USP, Opadry White [redacted] Ethyl Cellulose [redacted]) and Hard Gelatin Capsules. Each capsule contains [redacted] 60 mg of trospium chloride.

Sanctura XR Capsules are packaged in HDPE bottles. The bottles contain 30 capsules. Each bottle contains a silica gel desiccant canister.

Trospium chloride is a colorless or slightly yellowish, fine crystalline Its identity has been established by Trospium chloride is freely soluble in water.

Trospium chloride drug substance was originally obtained from The source was changed to Drug substance information is cross-referenced to DMF and

The applicant has submitted sufficient information to demonstrate that trospium chloride from both sources is identical.

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

Sanctura XR is indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency and urinary frequency. The recommended dose is one 60-mg capsule daily in the morning. Sanctura XR should be taken with water on an empty stomach at least one hour prior to a meal.

Sanctura is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, or patients who are at risk of these conditions. Patients who have demonstrated hypersensitivity to any of the components of the product should not take Sanctura.

C. Basis for Approvability or Not-Approval Recommendation

Adequate controls for raw materials are in place. Manufacturing processes are robust and adequately controlled. Specifications are adequate to ensure the identity, strength, quality, purity and potency of the drug product. Container/closure systems are adequate to protect the drug product. The dissolution specification has been tightened to conform to "Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations." The product is stable over the proposed shelf life (24 months) when stored at controlled room temperature.

Labeling is acceptable. All deficiencies have been resolved. The Office of Compliance has made an overall recommendation of Acceptable.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS.

B. Endorsement Block

Gene W. Holbert/05-JUL-2007
Moo-Jhong Rhee/26-JUL-2007

C. CC Block

Regulatory Project Manager:	Jean R. Makie
Pharmaceutical Assessment Lead:	Donna F. Christner
Project Manager for Quality:	Linda Mullins-Athey

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/s/

Gene Holbert
7/26/2007 02:03:26 PM
CHEMIST

Moo-Jhong Rhee
7/26/2007 03:11:15 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-103
Applicant:	Indevus Pharmaceuticals, Inc.
Stamp Date:	13-Oct-2006 (Posted 18-Oct-2006)
PDUFA Date:	13-Aug-2007
Trademark:	Sanctura XR
Established Name:	Trospium chloride extended release capsules
Dosage Form:	Capsule. — 60 mg
Route of Administration:	Oral
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

NDA 22-103 is for a line extension to the currently approved 20-mg twice-daily (BID) tablet formulation of trospium chloride, marketed under the tradename Sanctura (NDA 21-595, approved May 2004). Studies for the extended-release capsule formulation (— 60 mg) have been performed under IND 71,305.

The drug product is an extended-release capsule that contains —

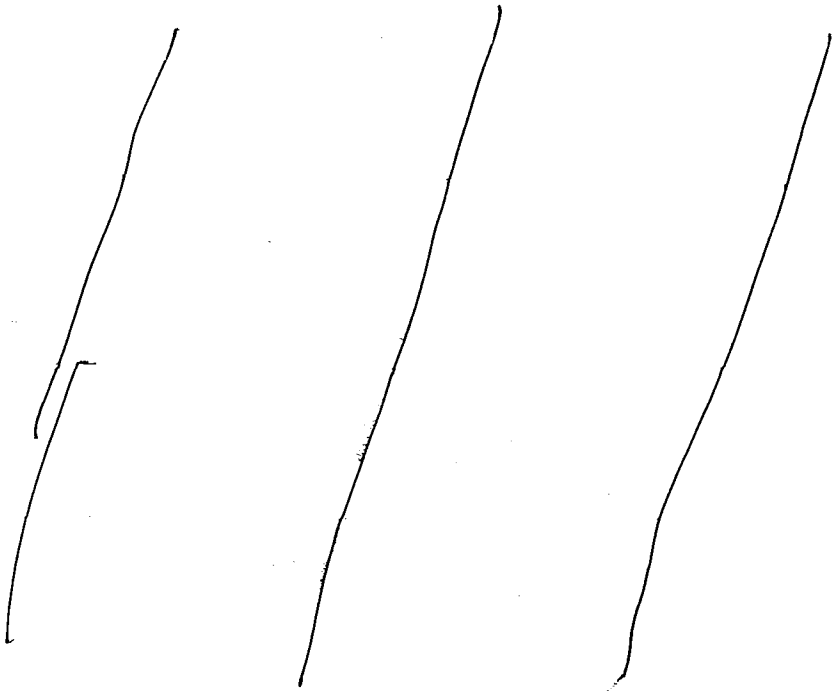
— Capsules will be packaged — into HDPE bottles with child resistant closures containing a desiccant —

The drug substance is trospium chloride, which is sourced from two different manufacturers. The drug substance from — is used in the currently approved 20 mg immediate release Sanctura tablets, and was used to manufacture the extended release formulation for Phase 2 clinical trials. Drug substance sourced from — was used in the Phase 3 clinical trials for Sanctura XR and in the stability samples. The sponsor has provided a comparison of drug substance from both sources, as recommended during development.

B. Critical issues for review

The equivalence of drug substance sourced from two different manufacturers will need to be evaluated during the review. In addition, the DMF for drug substance supplied by — will need to be reviewed. The sponsor has performed a dissolution comparison of one drug product lot manufactured with — drug substance against 5 drug product lots manufactured using — drug substance, for which the sufficiency will need to be evaluated. **Sponsor was advised at the preNDA meeting held 14-Sep-2006 that if the drug substances were not determined to be comparable, then stability data on drug product manufactured using the — drug substance would be required.**

For manufacturing, —



C. Comments for 74-Day Letter

We acknowledge submission of the comparison of the — and — drug substances in the NDA. This information is currently under review. We remind you of our advice given at the preNDA meeting held 14-Sep-2006 that if the drug substances were not determined to be comparable, then stability data on drug product manufactured using the — drug substance would be required. We will advise you if additional stability data is required once this determination has been made.

We acknowledge your request to discontinue — testing. —

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.

D. Recommendation:

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

Donna F. Christner, Ph.D.

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
X		On its face, is the section organized adequately?	
X		Is the section indexed and paginated adequately?	
X		On its face, is the section legible?	
X		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
X		Has an environmental assessment report or categorical exclusion been provided?	Exclusion as per 21 CFR 25.31(b)

B. Technical Checklists;

1. Drug Substance

X		Does the section contain synthetic scheme with in-process parameters?	DMF DMF
X		Does the section contain structural elucidation data?	DMF DMF
X		Does the section contain specifications?	DMF DMF
X		Does the section contain information on impurities?	DMF DMF
X		Does the section contain validation data for analytical methods?	DMF DMF
X		Does the section contain container and closure information?	DMF DMF
X		Does the section contain stability data?	DMF DMF

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	
X		Does the section contain quality controls of excipients?	
X		Does the section contain information on composition?	
X		Does the section contain specifications?	
X		Does the section contain information on degradation products?	
X		Does the section contain validation data for analytical methods?	
X		Does the section contain information on container and closure systems?	
X		Does the section contain stability data with a proposed expiration date?	24 months
X		Does the section contain information on labels of container and cartons?	Draft labels
X		Does the section contain tradename and established name?	

C. Review Issues

X		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	X	Is a team review recommended?	
X		Are DMFs adequately referenced?	

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/s/

Donna Christner
12/1/2006 04:06:29 PM
CHEMIST

Moo-Jhong Rhee
12/4/2006 10:03:30 AM
CHEMIST
Chief, Branch III