

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-103

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-103

SUPPL #

HFD # 580

Trade Name Sanctura XR

Generic Name trospium chloride extended release capsules, 60 mg

Applicant Name Indevus Pharmaceuticals, Inc.

Approval Date, If Known August 3, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 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 NO

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

3 years

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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 NO

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

NDA# 21-595

Sanctura (trospium chloride) 20 mg

NDA#

NDA#

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

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 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 8:

(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

(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

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

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:

IP631-018 and IP631-022

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

Investigation #2 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:

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

Investigation #2 YES NO

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

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"):

IP631-018 and IP631-022

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 # 71,305 YES ! NO
! Explain:

Investigation #2 !
IND # 71,305 YES ! 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?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(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

If yes, explain:

Name of person completing form: Jennifer Mercier
Title: Chief, Project Management Staff
Date: August 3, 2007

Name of Office/Division Director signing form: Mark Hirsch, M.D.
Title: Acting Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Jennifer L. Mercier
8/3/2007 01:43:13 PM

Mark S. Hirsch
8/3/2007 03:59:54 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-103 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: October 13, 2006 PDUFA Goal Date: August 13, 2007 (Approval action taken on August 3, 2007)

HFD 580 Trade and generic names/dosage form: Sanctura XR™ (trospium chloride extended-release capsules) 60 mg

Applicant: Indevus Pharmaceuticals, Inc.

Therapeutic Class: Antimuscarinic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only):

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One (1)

Indication #1: Treatment of Overactive Bladder (OAB)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

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

- Yes: Please proceed to Section A.
 No: Please check all that apply: 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: A pediatric waiver was previously granted for trospium chloride tablets (NDA 21-595).

The Division, therefore, grants a full waiver
for trospium chloride extended release capsules.

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 (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ 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
- Other: _____

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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.

NDA 22-103

Page 3

This page was completed by:

{See appended electronic signature page}

Ayoub Suliman, R.Ph., Pharm.D.
Regulatory Health Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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

/s/

Mark S. Hirsch
8/3/2007 01:58:45 PM

NDA 22-103

Sanctura XR (trospium chloride extended release capsules, 30mg and 60mg)

Debarment Information

See "NDA Regulatory Filing Review" prepared by PM and filed under "Administrative Review-Filing" section of this Action Packet.

NDA 22-103

Sanctura XR (trospium chloride extended release capsules, 60mg)

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 22-103	Efficacy Supplement Type SE- N/A	Supplement Number: N/A
Drug: trospium chloride extended release capsules		Applicant: Indevus Pharmaceuticals, Inc.
RPM: Jean Makie, M.S., R.D.		HFD-580 Phone # 301-796-0952
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		IS
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		August 13, 2007
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (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).		<input type="checkbox"/> 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)		N/A
• Status of advertising (approvals only)		() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		() Yes (X) 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
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		X
❖ 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		X; none requested
• 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
• Pre-NDA meeting (indicate date)		X
• Pre-Approval Safety Conference (indicate date; approvals only)		N/A (no significant safety concerns)
• 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
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	X
❖ 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 clinical review)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	X
❖ Biopharmaceutical review(s) (indicate date for each review)	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	X
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X (EA acceptable; See Chemistry Review)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	(X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	X
❖ CAC/ECAC report	X

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

/s/

Ayoub Suliman
8/7/2007 12:39:33 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: July 31, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: Teleconference minutes regarding DRUP and DMETS request for carton/container revisions	
Total no. of pages including cover: 4	

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED,
CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, or a person authorized to deliver this document to the
addressee, you are hereby notified that any review, disclosure, dissemination, copying, or
other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 796-
0952. Thank you.

MEMORANDUM OF TELECON

DATE: July 31, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President Regulatory Affairs

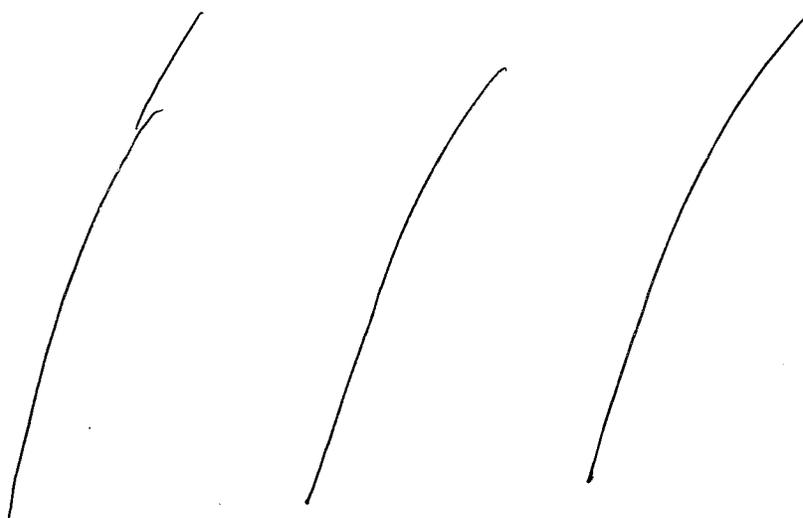
AND

Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, Division of Reproductive and Urologic Products (DRUP)

SUBJECT: NDA 22-103: DRUP and DMETS request for revisions to container and carton labels

Teleconference Discussion: The Sponsor was notified that the Division and DMETS had additional requests for revisions to the proposed container and carton labels for Sanctura XR. The Sponsor was informed that these requests would be sent to them via this fax.

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



(A)

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

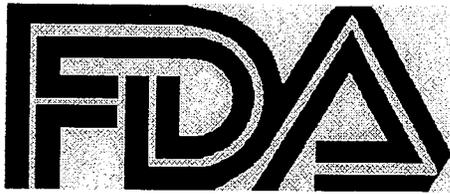
Deliberative Process

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

/s/

Jean Makie
7/31/2007 11:42:28 AM
CSO

Jean Makie
7/31/2007 11:48:45 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: June 29, 2007, teleconference (DMETS recommendations) are attached	

Total no. of pages including cover:

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you
are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-0952. Thank you.

MEMORANDUM OF TELECON

DATE: June 29, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.

DRUG/INDICATION: Trosipium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President Regulatory Affairs

AND

Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, Division of
Reproductive and Urologic Products (DRUP)

SUBJECT: NDA 22-103: DMETS and DDMAC recommendations and comments

Teleconference Discussion: The Division conveyed the following comments and recommendations provided by DMETS and DDMAC regarding the Sponsor's proposed trade names, and Sanctura XR.

- DMETS does not recommend the use of the proprietary name _____ DMETS specifically objects _____

- DMETS does not object to the use of the proprietary name, "Sanctura XR." DMETS acknowledges the potential for error on initial introduction to the marketplace with Sanctura. However, Sanctura and Sanctura XR do not share overlapping strengths or dosing frequency, which may help to limit this confusion and error.
- However, despite these differences, DMETS recommends that the sponsor institute an educational program to help practitioners be aware of the presence of the new extended-release product. In addition, DMETS recommends implementation of the label and labeling revisions outlined below in order to minimize potential errors with the use of this product.

3

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

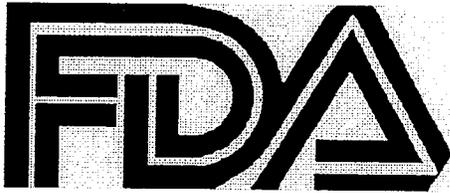
Deliberative Process

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

/s/

Jean Makie
6/29/2007 12:17:47 PM
CSO

Jean Makie
6/29/2007 12:26:27 PM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 28, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: June 27, 2007, teleconference (CMC request) are attached	

Total no. of pages including cover:

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

MEMORANDUM OF TELECON

DATE: June 27, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.,

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President Regulatory Affairs
Raj Mahi, Ph.D.

AND

Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, Division of
Reproductive and Urologic Products (DRUP)
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Branch III, Pre-
Marketing Assessment Division II, ONDQA
Gene Holbert, Ph.D., Chemistry Reviewer, Branch III, Pre-Marketing Assessment
Division II, ONDQA
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical
Pharmacology (OCP) @ DRUP

SUBJECT: NDA 22-103: Request for tightening of dissolution specifications for release and stability of drug product

Teleconference Discussion: The Division requested this teleconference to discuss the Sponsor's current proposed dissolution specifications of $\pm 15\%$. According to the Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, section VII.B.1, the dissolution specifications for drug product release and stability should be no more than $\pm 10\%$ (reasonable deviations are acceptable provided that the range at any time point does not exceed 25%). The Division requested that the Sponsor evaluate their existing release and stability data to propose revised dissolution specifications that are more consistent with the recommendations in this guidance.

Sponsor Response: The Sponsor committed to reevaluating the release and stability data and agreed to submit a revised proposal for dissolution specifications based on this review. The Sponsor stated that, based on a cursory review of the data, they believe that the dissolution specifications can be adjusted to within the $\pm 10\%$ range.

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

/s/

Jean Makie
6/28/2007 10:38:08 AM
CSO

Donna Christner
6/28/2007 10:47:12 AM
CHEMIST



INFORMATION REQUEST LETTER

NDA 22-103

Indevus Pharmaceuticals, Inc.
Attention: John Berryman, M.S.
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Berryman:

Please refer to your October 12, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for trospium chloride extended release for the treatment of overactive bladder.

We continue our review of your application and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Justify the lack of limits for the degradation product, _____
2. Explain why you have proposed a dissolution specification of _____ at 16 hours when the amount dissolved at 12 hours is already well above _____
3. The information in section _____ DMF _____ s. Submit the correct _____ 1 refers to _____

4. The only information on photostability testing is found in tables 1-3 in section 3.2.8 Stability. It is not clear from those tables how the samples were exposed. Submit a more thorough description of the photostability study.
5. Sugar spheres are not listed as an ingredient in the package insert. Add sugar spheres as an ingredient in the Description section of the package insert.

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at 301-796-0952.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
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/

Moo-Jhong Rhee
5/4/2007 04:37:59 PM
Chief, Branch III



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: April 24, 2007, teleconference (re: PPI revisions and trade name proposal) are attached	

Total no. of pages including cover: 4

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

MEMORANDUM OF TELECONFERENCE

DATE: April 24, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.,

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

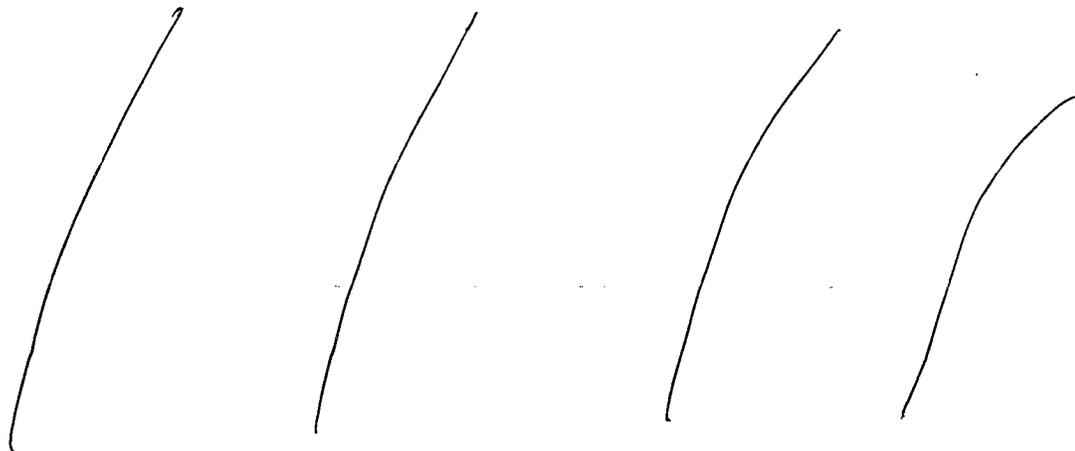
BETWEEN: John Berryman, M.S., Vice President, Regulatory Affairs

AND

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

SUBJECT: NDA 22-103: Recommendations regarding the Patient Package Insert (PPI) and additional information Trade name proposal

Teleconference Discussion: PPI revisions: CAPT Makie conveyed to the Sponsor the following comments and recommendations from the Division of Surveillance, Research, and Communication Support (DSRCS) regarding the Sponsor's proposed PPI submitted on March 19, 2007:



Sponsor response: The Sponsor agreed to submit a revised PPI and Full Prescribing Information (FPI), accordingly.

Trade Name Proposal: Ms. Makie asked the Sponsor for an update regarding the Division's previous requests discussed on an April 3, 2007 teleconference:

- Submit supporting documentation (e.g., marketing studies, focus groups, etc.) for the trade name proposal _____ that was included in the February 21, 2007, submission.
- Consider submitting one to two additional trade name proposals, with supporting documentation, for review.

The Division's concerns regarding possible medication errors related to the proposed _____ trade name were reiterated. It was also reemphasized that the Agency can approve labeling for a product without approval of a trade name. The Sponsor was reminded that DMETS and DDMAC review trade name proposals within 90-days of an action.

Sponsor response: The Sponsor stated that they continue their deliberations regarding focus group testing of _____ as well as consideration of alternative trade name proposals, with their marketing partner. The Sponsor agreed to submit (with the revised PPI submission) either a statement that such marketing studies were not or will not be completed for focus group testing of _____. The Sponsor also stated that additional trade name proposals will be discussed internally and such proposals (with justifications) will be submitted should they become available. The Sponsor also agreed to submit a timeline for submission of such proposals with the PPI submission.

Revised Carton/Container Mockups: The Sponsor was reminded to submit revised color container and carton mockups to be consistent with the current trade name proposal, _____

Sponsor response: The Sponsor stated that they continue to have discussions of color selection for carton and containers with their marketing partner. The Sponsor agreed to submit black and white mockups of _____ immediately and will follow up with color mockups as soon as feasible for either _____ or an alternative trade name proposal, as appropriate.

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

/s/

Jean Makie
4/26/2007 09:30:10 AM
CSO

Jean Makie
4/26/2007 09:33:58 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: April 3, 2007, teleconference (re: FPI formatting changes and trade name proposal) are attached	
Total no. of pages including cover: 4	

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

NDA 22-103: April 3, 2007 Teleconference memo

MEMORANDUM OF TELECONFERENCE

DATE: April 3, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.,

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President, Regulatory Affairs

AND

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

SUBJECT: NDA 22-103: Formatting recommendations regarding the Full Prescribing Information (FPI) and additional information Trade name proposal



Sponsor response: The Sponsor agreed to submit a revised FPI accordingly.

Trade Name Proposal: Ms. Makie conveyed the Division's following requests

NDA 22-103: April 3, 2007 Teleconference memo

- Submit supporting documentation (e.g., marketing studies, focus groups, etc.) for the trade name proposal _____ that was included in the February 21, 2007, submission.
- Consider submitting one to two additional trade name proposals, with supporting documentation, for review.

Sponsor response: The Sponsor stated that focus group testing was not completed for the proposed _____ trade name, _____

_____. The Sponsor also stated that additional trade name proposals will be discussed internally and such proposals (with justifications) will be submitted should they become available.

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

/s/

Jean Makie
4/3/2007 11:28:25 AM
CSO

Jean Makie
4/3/2007 11:33:44 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: NDA 22-103: March 5, 2007, teleconference (PPI request) are attached	

Total no. of pages including cover:

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you
are hereby notified that any review, disclosure, dissemination, copying, or other action based on the
content of this communication is not authorized. If you have received this document in error, please
notify us immediately by telephone at (301) 796-0952. Thank you.

MEMORANDUM OF TELECON

DATE: March 5, 2007

APPLICATION NUMBER: NDA 22-103

SPONSOR: Indevus Pharmaceuticals, Inc.,

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President Regulatory Affairs

AND

Jean Makie, M.S., R.D.

Sr. Regulatory Project Manager

Division of Reproductive and Urologic Products (DRUP)

SUBJECT: NDA 22-103: Request for Patient Package Insert (PPI) submission

Teleconference Discussion: Ms. Makie telephoned the Sponsor to convey the Division's request that they submit a proposed PPI for this product. Approved labeling for Sanctura (trospium chloride; NDA 21-595) includes a PPI. The Sponsor agreed to submit a proposed PPI to NDA 22-103.

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

/s/

Jean Makie
3/7/2007 10:20:32 AM
CSO

Jean Makie
3/7/2007 10:27:41 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2007

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952

Subject: NDA 22-103: March 1, 2007 teleconference (statistics) minutes are attached

Total no. of pages including cover:

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

MEMORANDUM OF TELECON

DATE: March 1, 2007

APPLICATION NUMBER: NDA 22-103 **SPONSOR:** Indevus Pharmaceuticals, Inc.,

DRUG/INDICATION: Trospium chloride extended release for the treatment of overactive bladder (OAB)

BETWEEN: John Berryman, M.S., Vice President Regulatory Affairs
Ute Schwiderski, Ph.D., Vice President Biostatistics and Data Management

AND

Jean Makie, M.S., R.D.
Sr. Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)
Mahboob Sobhan, Ph.D., Biometrics Team Leader, Division of Biometrics II @
DRUP

SUBJECT: NDA 22-103: Discussion of data definitions

Teleconference Discussion: The Division requested this teleconference to clarify data definitions submitted in NDA 22-103. The Sponsor clarified the variables and related data dictionary acronyms used to define datasets submitted for the primary Phase 3 efficacy studies. No further statistical or dataset information was requested at this time.

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

/s/

Jean Makie
3/7/2007 10:04:53 AM
CSO

Jean Makie
3/7/2007 10:17:14 AM
CSO

**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 22-103 Requested Tradename: Sanctura XR

Generic: trospium chloride extended release capsules — 50 mg)

Date of Application: October 12, 2006
Date of Receipt: October 13, 2006
PDUFA Date: August 13, 2007
Action Goal Date: August 13, 2007

Indication(s) requested: for the treatment of overactive bladder

Type of Application: Full NDA X 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) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES X NO _____
User Fee ID# 3006775
Clinical data? YES X NO _____ Referenced to NDA#

Date clock started after UN N/A

User Fee Goal date: August 13, 2007

Action Goal Date (optional) August 13, 2007

- 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

If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO
 - 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:
- The sponsor requested in this NDA 22-103 submission a waiver for all ages of pediatric patients. Background information: The Approval Letter, dated May 28, 2004, for Sanctura (NDA 21-595) granted a partial waiver of pediatric studies for ages 4 and younger and it deferred pediatric studies or the treatment of overactive bladder in pediatric patients ages 5 to 15 years. On April 11, 2006, a waiver for pediatric studies for NDA 21-595 was granted under section 4 of the Pediatric Research Equity Act. _____

- 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: 71,305

End-of-Phase 2 Meeting? Date 8/1/05
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date 9/14/06
 If yes, distribute minutes before filing meeting.

Project Management

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

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

Requested Tradename: Sanctura XR

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

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

*N/A: This is not an application for an OTC product.

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?
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES YES NO NO

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

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES N/A

If 505(b)(2), complete the following: Not applicable

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

FILING MEETING MINUTES TO BE ATTACHED

NDA 22-103: Filing Meeting Minutes

NDA: 22-103

Sponsor: Indevus Pharmaceuticals

Drug: Sanctura XR (trospium chloride extended release capsules, 60 mg)

Date: November 30, 2006

Time: 11:00 AM– 12:00 PM

FDA/CDER/DRUP Attendees:

Mark Hirsch, M.D., Medical Team Leader and Acting Deputy Division Director,
Division of Reproductive and Urologic Products (DRUP)
Harry Handelsman, D.O., Medical Reviewer, DRUP
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical
Pharmacology (OCP) @ DRUP
Martin Kaufman, Project Manager, DRUP
Laurie McLeod-Flynn, Ph.D., Pharmacology/Toxicology Reviewer, DRUP
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Initial Quality Assessment
Branch III, Pre-Marketing Assessment Division II @ DRUP
Mahboob Sobhan, Biometrics Team Leader, Division of Biometrics 2, Office of
Biostatistics @ DRUP
Roy Blay, Division of Scientific Investigation (DSI) [via phone]

Background: On October 12, 2006, a new drug application (NDA 22-103) was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sanctura XR (trospium chloride extended release capsules, 60 mg) for the treatment of overactive bladder. Unless we notify the Sponsor within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 13, 2007.

Issues Discussed: During this filing review meeting, the following issues were discussed:

Clinical

- The application is fileable. The Medical Officer presented a summary of efficacy and safety results.

The following review issue was identified and will be conveyed to the Sponsor in the 74-Day letter.

- The incidence and severity of reported adverse events of constipation will be a review issue.

- Identify raw efficacy data files and derived analyses files for efficacy.

Pharmacology/Toxicology

- The application is fileable.
- No review issues were noted at time of filing.
- It was determined that the in vitro metabolism study reports submitted in this NDA for Sanctura XR are the same as those included in the original Sanctura NDA (NDA 21-595) and previously reviewed under that application.

Chemistry

- The application is fileable.

The following review issues were identified and will be conveyed to the Sponsor in the 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 pre-NDA meeting held September 14, 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. _____
_____, Microbiology will be consulted on whether or not the request to discontinue _____ testing on stability should be approved.
- 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.

Regulatory

- The application is fileable.
- The Sponsor's Full Prescribing Information (FPI) was reviewed for regulatory compliance to the new Physician Labeling Rule. The Project Manager's review was discussed with Jeanne Delasko, SEALD reviewer and appropriate changes, as recommended, have been incorporated into the comments below.

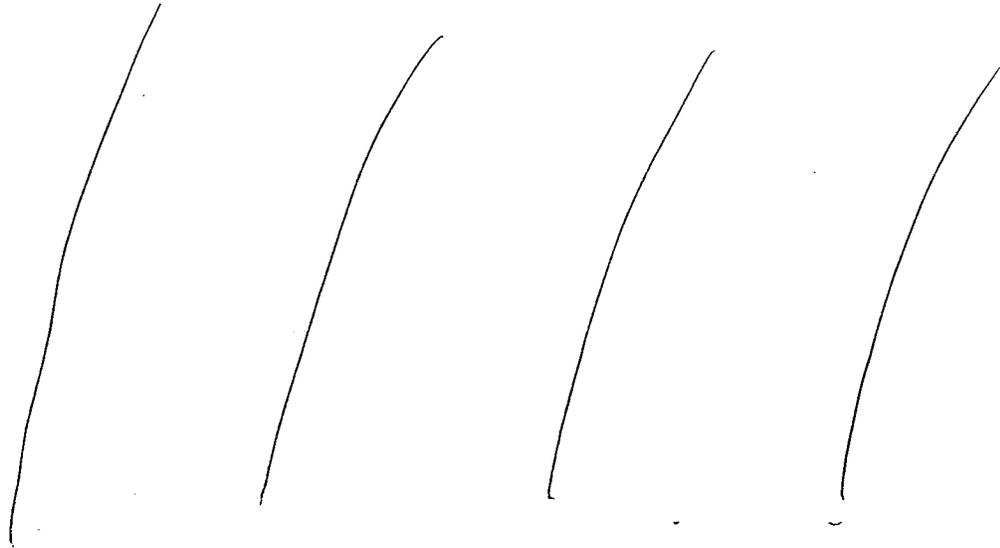
The following comments regarding the FPI will be conveyed to the Sponsor in the 74-Day Letter:

2 Page(s) Withheld

 / Trade Secret / Confidential

 Draft Labeling

 Deliberative Process



Internal Consults:

The following consults will be sent:

- The FPI and proposed tradename (Sanctura XR) will be sent to the Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Medication Errors and Technical Support (DMETS).
- The FPI will be sent to the Division of Surveillance, Research, and Communication Support (DSRCS).
- Clinical site inspection(s) are deemed not necessary at this time. If irregularities in the data become evident, then a DIS consult will be re-considered.
- A consult will be sent to Microbiology.

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

/s/

Mark S. Hirsch
12/22/2006 11:38:53 AM

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

/s/

Jean Makie
1/10/2007 11:45:14 AM
CSO

Jean Makie
1/10/2007 11:45:46 AM
CSO

- As discussed during your pre-NDA meeting, we remind you to submit the population pharmacokinetic (PK) data and the population PK summary report from the Phase 3 clinical trial IP631-018.
- Submit the following datasets that could not be located in the NDA in SAS transport file format:
 - PK parameters for individual subjects of IP631-019 and IP631-020.
 - Drug concentrations for individual subjects of Phase 2 clinical trial IP631-016.
- _____
- Dosing in the presence of alcohol will be a review issue.

Statistics

- Identify raw efficacy data files and derived analyses files for efficacy.

Chemistry

- 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 at your pre-NDA meeting that if the drug substances were not determined to be comparable, 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. _____
_____, Microbiology will be consulted on whether or not your request to discontinue _____ testing on stability is acceptable.
- 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.

Regulatory

We are providing you with the following comments regarding your proposed Full Prescribing Information (FPI). Submit a revised FPI accordingly.

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

- Be aware that further modifications to the content of your labeling will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at (301) 796-0952.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Acting Deputy Director
Division of Reproductive and Urologic 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/

Mark S. Hirsch
12/22/2006 11:07:32 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-103

NDA ACKNOWLEDGMENT

Indevus Pharmaceuticals, Inc.
Attention: John Berryman, M.S.
Vice President, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421-7971

Dear Mr. Berryman:

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:	Sanctura XR™ (trospium chloride extended release)
Review Priority Classification:	Standard (S)
Date of Application:	October 12, 2006
Date of Receipt:	October 13, 2006
Our Reference Number:	NDA 22-103

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 13, 2007.

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. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies to be conducted in 0-16 year old children for this application. Once the application has been filed, we will notify you whether we have waived and/or deferred the pediatric study requirements for this application.

NDA 22-103

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Jean Makie, M.S., R.D., Sr. Regulatory Project Manager, at (301) 796-0952.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic 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/

Margaret Kober
11/7/2006 09:32:43 AM
Chief, Project Management Staff



Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION III

FACSIMILE TRANSMITTAL SHEET

DATE: October 12, 2006

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, M.S., R.D. Sr. Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: IND 71,305: FDA Minutes for the September 14, 2006 Pre-NDA Teleconference are attached	
Total no. of pages including cover:	

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED,
CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, or a person authorized to deliver this document to the
addressee, you are hereby notified that any review, disclosure, dissemination, copying, or
other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 796-
0952. Thank you.

Type B Pre-NDA Teleconference

Date: September 14, 2006

Time: 10:00 – 11:30 AM

Sponsor: Indevus Pharmaceuticals, Inc.

IND: 71,305

Drug: trospium chloride, modified release formulation

CDER participants:

Mark Hirsch, M.D., Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)

George Benson, M.D., Medical Team Leader, DRUP

Suresh Kaul, M.D., Medical Reviewer, DRUP

Ameeta Parekh, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader,
Office of Clinical Biopharmaceutics (OCB) @ DRUP

Sandhya Apparaju, Ph.D., Clinical Biopharmaceutics Reviewer, OCB @ DRUP

Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Initial Quality Assessment
Branch III, Pre-Marketing Assessment Division II @ DRUP

Laurie Mcleod-Flynn, Ph.D., Pharmacology/Toxicology Reviewer, DRUP

Mahboob Sobhan, Ph.D., Biometrics Team Leader, Division of Biometrics II @ DRUP

Jean Makie, M.S., R.D., Sr. Project Manager, DRUP

From Indevus Pharmaceuticals, Inc.

Bobby W. Sandage, Jr., Ph.D., Executive Vice President R & D

John Berryman, M.S., Vice President Regulatory Affairs

James Shipley, M.D., Senior Vice President, Clinical Development and Medical Affairs

LuAnn Sabounjian, Vice President Clinical Development

Laura Koller, M.S., Senior Clinical Project Manager

Ute Schwiderski, Ph.D., Vice President Biostatistics and Data Management

Mark Harnett, M.S., Executive Director Biostatistics and Data Management

Andreas Woppmann, Ph.D., Vice President Pharmaceutical Development, Operations &
Quality

Rajesh Mahey, Ph.D., Senior Director Pharmaceutical Technology

Mark Roessel, Senior Director Regulatory Affairs

From Esprit Pharma (Co-marketing partner)

Ernie Biczak

Sponsor Questions and FDA Responses

1. At the End of Phase 2 meeting with the Division held on 01 August 2005, the Division recommended that the safety data for at least 100 subjects treated for \geq 12 months with Sanctura XR be submitted in the 4-month Safety Update. The Sponsor voluntarily proposed that additional population pharmacokinetics would be completed for 250 subjects. The Sponsor plans to submit both the long term safety data and the population pharmacokinetics data in the 4 month Safety Update. The Sponsor wishes to confirm that this is acceptable.

Division Response:

Clinical

Submission of the agreed-upon long term safety data (100 patients treated for \geq 12 months) in the 4 month safety update is acceptable. We also acknowledge your intent to submit safety data on at least 300 patients exposed for \geq 6 months in the initial NDA submission.

Please be aware that the DRAFT Guidance for Review Staff and Industry for Good Review Management Principles and Practices (GRMP) states that "...it is important for the applicant to provide a complete application at the time of initial submission...". However, the GRMP also states that "...the focus on initial submission of a complete application does not preclude agreements between an applicant and a Division on a postsubmission planned amendment...". While we confirm our EOP2 agreement to accept the long-term safety data with the 4-month safety update, you should be aware that safety concerns arising from the 4-month SU may be difficult to resolve within the remaining clock and could threaten first cycle approval.

Clinical Pharmacology

Yes, it is acceptable to submit the population pharmacokinetic (PK) data analysis at 4 months into the review cycle. However, due to the logistical considerations involved in a review process (e.g., the need for a pharmacometric consult, etc.), any data that is critical for final labeling should ideally be submitted at the time of initial NDA submission to allow a thorough and timely review.

2. At the August 2005 End of Phase 2 meeting, the Division agreed that, if plasma levels for trospium and major trospium metabolites for Sanctura XR were similar to or lower than those for Sanctura BID, the existing safety data contained in NDA 21-595 would provide additional support for the Sanctura XR NDA. The current data show that the levels for trospium and major metabolites for Sanctura XR are similar to or lower than the BID formulation. Thus, the Sponsor wishes to confirm that long term safety data from NDA 21-595 can be used to support the XR formulation NDA.

Division Response: We confirm that the existing safety data from NDA 21-595 can provide additional support for the Sanctura XR NDA if data shows that the levels of trospium and major trospium metabolites are similar or lower than those for Sanctura BID.

However, we believe that the agreed-upon 6-month and 1-year safety data for Sanctura XR is still a very important part of the Sanctura XR NDA. One reason to have an adequate stand-alone safety database for Sanctura XR is to address concerns related to gut motility. Summary data provided for Studies 018 and 022 in your meeting package appear to demonstrate a 4 to 5-fold increase in incidence of constipation in the Sanctura XR-treated group compared to placebo.

3. In the minutes to the August 2005 End of Phase 2 meeting the Division noted that, "It is not anticipated that additional nonclinical studies would be required to support filing an NDA; however, the Division may request additional studies if unexplained toxicity, exaggerated pharmacology, or unqualified metabolites are observed or if impurity levels exceed the qualification limits." The current clinical trial data from studies in over 600 patients receiving Sanctura XR shows that no such events have occurred. Therefore, the Sponsor wishes to reference the existing nonclinical data from NDA 21-595 in the Sanctura XR submission. Please confirm that the application of the existing nonclinical studies of trospium chloride to the NDA is acceptable to the Division.

Division Response: Yes, application of the existing nonclinical studies of trospium chloride to the NDA is acceptable to the Division.

4. The Sponsor asks if it is necessary to resubmit the individual nonclinical study reports and publications from NDA 21-595 in the new CTD submission or if it is preferable to reference the existing NDA?

Division Response: It is not necessary to resubmit studies previously submitted to NDA 21-595 with the new CTD.

5. The Division asked the Sponsor in the Sanctura XR End of Phase 2 meeting if the excipient _____ has been characterized in nonclinical studies. The Sponsor provided information about _____ including a summary of the toxicological data, in an IND amendment (serial 013, 05 August 2005). Is the information provided in the IND amendment adequate to respond the Division's request?

Division Response: Yes, the information provided is adequate.

6. A supplement was submitted to NDA 21-595 (S-002) on 23 January 2006 for a labeling change based on a clinical study of the interaction of trospium chloride with digoxin. This study measuring pharmacokinetic parameters of both digoxin and Sanctura during concomitant use demonstrated that the plasma, serum and urine pharmacokinetics of each are unaffected by the presence of the other drug. It is the Sponsor's intention to apply these study results to the Sanctura XR drug product as well and to include similar language in our draft labeling. Is this acceptable?

Division Response: Yes, this is acceptable.

7. The Sponsor plans to submit an NDA in CTD format. An outline of the CTD will be provided in the pre-meeting package. This NDA in CTD format will be filed electronically (though not as an e-CTD) in accordance with FDA guidances on submission in electronic format. The Sponsor plans to submit a paper copy of Modules 1 and 2. Does the Division have any comments or recommendations regarding the planned format of the submission?

Division Response: The planned format is generally acceptable. We request the following additions:

Clinical

- **A Summary of discontinuations due to adverse events in the Module 2 Summary of Clinical Safety.**
- **A separate Summary in the Module 2 Summary of Clinical Safety just for constipation and urinary retention/UTI adverse events.**

Biometrics

- **Provide analyses files for efficacy including data definitions of derived variables.**

8. During a monitoring visit at one of the Phase 3 clinical trial sites it was discovered that source documents had been altered at the site. A full audit of the site was conducted and upon review of the audit findings Indevus decided to close

the site and to report the auditor's findings to the FDA Division of Scientific Investigations. This report was made on April 26, 2006. The site had enrolled 8 patients in the study. The Sponsor wishes to review with the Division the handling of the data from this site. The Sponsor proposes that the full ITT analysis will include all the data from this site. The Sponsor further proposes to run the two primary efficacy variables excluding the data from this site. If the resulting analysis is no different from the full ITT analysis we will leave the ITT results as they are. If the study outcome is different, we will drop the site's data from all the analyses (including safety) and rerun the entire study data excluding this site. In other words, if the suspect data from this site are sufficient to influence the outcome of the study the Sponsor will not allow the site study data to be used. In all cases the data from this site will remain in the SAS transport files in the NDA. Is this approach acceptable?

Division Response: No, this approach is not acceptable. We recommend that you not include the data generated from this particular site in the efficacy analysis. However, for completeness of the submission, the efficacy raw data from this site should be submitted for our review. Additionally, the safety data generated from this site should be included in all safety analyses.

Additional Discussion: After further discussion, the Division concluded that the Sponsor's approach outlined in Question 8 was acceptable.

9. The Sponsor intends to include two sources of the drug substance in the NDA: _____ and _____. The drug substance in the currently marketed product is provided by _____.

The Phase 3 clinical studies of Sanctura XR were conducted with drug substance made by _____ and the stability data for the new NDA will be on drug product made with _____ API. A DMF reference letter will be provided from both drug substance suppliers in the NDA. The Sponsor proposes to provide comparative dissolution data for the finished drug product, Sanctura XR, made with drug substance from each supplier. Is this satisfactory in order to use both suppliers commercially or is it necessary to cross reference or include any of the drug substance information from NDA 21-595 on the currently qualified supplier _____.

Division Response: No. In order to use two different drug substance suppliers, it will need to be shown that both suppliers manufacture comparable drug substances. Determination of comparability between drug substances manufactured by different suppliers will require review of the corresponding DMFs upon submission of the NDA. This will include comparison of the structure, physical characteristics, impurity profile, polymorphs, and particle size. If it is determined after the review of the DMFs that drug substance from both suppliers are comparable, then

comparative dissolution of drug product manufactured using the drug substance from the two different suppliers would be adequate. If it is not determined that the two drug substances are comparable other than the structure, stability data on drug product manufactured using the alternate drug substance supplier will need to be provided.

Sponsor Response: The Sponsor agreed to submit the requested information in the NDA.

Additional Clinical Pharmacology Comments:

In the new NDA:

- Provide composition proportionality information and in vitro dissolution profile comparisons for the 20 mg and 60 mg capsule strengths.
- Address the robustness of the modified release formulation when concomitantly administered with alcoholic drinks.
- For the definitive PK study P631-020, also include:
 - Individual subject data
 - Linear plots of concentration vs. Time data
 - Cross-study comparisons of systemic exposure following: both doses of the 20 mg BID regimen vs. a single morning dose of the 60 mg XR formulation; provide concentration vs. time plots and tabulated PK parameter comparisons of the aforementioned data.

Additional Clinical Comments:

No summary efficacy data was provided in your meeting package. This precludes identification and discussion of potential efficacy review issues (e.g., size of the treatment effect, analysis methods, etc.). We recommend an additional meeting between the Sponsor and FDA prior to the submission of the initial NDA in order to discuss summary efficacy data that will support this NDA.

Efficacy Summary -- Sponsor Response: The Sponsor submitted an additional briefing package, dated September 11, 2006, containing a summary of their efficacy analyses. The Sponsor's supplemental briefing package did not contain any specific questions for the Division. The Division provided comments on page 49 of this briefing package, wherein the Sponsor discusses

Additional Clinical Pharmacology Comments:

- The dosing recommendations in special populations (geriatric, renal and hepatic impairment, etc.) should be appropriately justified in the NDA for Sanctura XR.

Additional Clinical Comments:

-

Additional Biometrics Comments:

- In this briefing package, the efficacy analyses are shown as non-parametric, rank order analyses rather than parametric analyses as stated in the Statistical Analysis Plan for both phase 3 studies. The use of non-parametric, rank order analysis should be appropriately justified in the NDA for Sanctura XR.

Sponsor's Responses: The Sponsor agreed to provide information in the NDA to support dosing recommendations in special populations and in special circumstances. They have not yet decided whether to _____ The Sponsor will also support the use of the non-parametric, rank order analysis.

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

/s/

Mark S. Hirsch
10/12/2006 09:50:40 AM



Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION III

FACSIMILE TRANSMITTAL SHEET

DATE: April 27, 2006

To: John Berryman Vice President, Regulatory Affairs	From: Jean Makie, Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Products
Fax number: 781-761-0451	Fax number: (301) 762-9897
Phone number: 781-402-3451	Phone number: (301) 762-0952
Subject: IND 71,305: FDA Minutes for the April 3, 2006 Type C meeting are attached	
Total no. of pages including cover:	

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0952. Thank you.

IND 71,305: FDA Meeting Minutes for April 3, 2006 Type C meeting

IND 71,305:

April 3, 2006 Type C Meeting Minutes

IND: 71,305 **Type C Guidance:** Indevus Urgency Severity Scale

Drug: Trospium chloride, modified release formulation

Sponsor: Indevus Pharmaceuticals

Date: April 3, 2006 **Time:** 1:00 – 2:30 PM

Location: White Oak Building, Room 1539

FDA Attendees:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Products
(DRUP)

George Benson, M.D., Medical Team Leader, DRUP

Suresh Kaul, M.D., Medical Officer, DRUP

Roger Wiederhorn, M.D., Medical Officer, DRUP

Mahboob Sobhan, Ph.D., Biostatistics Reviewer, DRUP

Jean Makie, M.S., R.D, Project Manager, DRUP

Laurie Burke, Director, Study Endpoints & Label Development Team (SEALD), Office
of New Drugs-Immediate Office (OND-IO)

Lilliam Rosario, Ph.D., Study Endpoints Reviewer, SEALD, OND-IO

Industry Attendees

From Indevus Pharmaceuticals, Inc.

Bobby W. Sandage, Jr., Ph.D., Executive Vice President, Research & Development

James Shipley, M.D., Senior Vice President, Clinical Development & Medical Affairs

Ute Schwiderski, Ph.D., Vice President, Biostatistics and Data Management

Mark Harnett, M.S., Senior Director, Biostatistics and Data Management

Laura Koller, M.S., Senior Clinical Project Manager

John Berryman, M.S., Vice President, Regulatory Affairs

Mark Roessel, Sr. Director, Regulatory Affairs

LuAnn Sabounjian, B.S.N, Vice President, Clinical Development

From Esprit Pharma

Ernie Biczak, M.D., Medical Affairs

Background: The Sponsor requested this Type C Guidance meeting on January 23, 2006. On January 31, 2006, the Sponsor submitted the following questions in their briefing package supplement to the Division. The Division's preliminary draft responses were supplied to the Sponsor on March 30, 2006. Discussions held during the meeting are summarized below in italics.

SPONSOR'S QUESTIONS:

- A. Does the Agency agree that a tool for quantitation of the OAB symptom "urgency" would be of use to physicians who treat OAB patients?

Division Response: Yes.

- B. In as much as the prospective validation of the IUSS as presented in the report to Study IP631-005 addresses the concerns of the Division over the retrospective validation presented in the report to Study IP631-008 and in fact further supports the earlier findings, and in light of the favorable data supporting validation of the IUSS in Studies IP631-008 and IP631-005, does the Agency agree that the results of these assessments support the validity of this tool as an endpoint for outcome in a clinical trial?

Division Response: No. The IUSS is not considered to be adequately validated because of clear deficiencies in: **content validity, construct validity, known-groups validity, and test-retest reliability.** Deficiencies in each of these psychometric tests are discussed below.

Content validity: On its face, the IUSS lacks content validity for the following reasons:

- It does not adequately represent the concepts and domains to be measured from the patient's perspective. As stated in the Draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, "... *instrument developers choose the concepts and domains to be measured based on patient interviews, along with reviews of the literature and expert opinion.*" Further, it is stated "*PRO instrument item generation is incomplete without patient involvement.*" In the case of the IUSS, the single-item was generated based solely upon a literature review and expert opinion, without patient involvement. Patient interviews were held only after the IUSS had been used in clinical trials. When focus groups ultimately were held, the objectives of these studies were not to develop a conceptual framework, nor to generate items from patients' own words; but instead

“To address...Patient definitions of the term “urge” and “urgency” in the context of OAB.” Prior to enrollment, before patients were given the opportunity to express their own feelings about their condition, focus group candidates were informed (as in Question 9 of the Background Questionnaire – highlighted in bold font) that *“Urgency means the sudden, intense desire to urinate that may be hard to control and could cause you to accidentally wet yourself.”* According to the study report, focus group patients actually described their symptoms as a “painful sensation” or “the bladder feeling full and requiring immediate relief”. It is not clear that patients would have used the word “urgency” to describe their feelings, had they not been informed beforehand.

- The IUSS uses jargon that is highly technical and not likely to be interpretable (e.g. such as “toilet void”, “degree of urgency” and “urgency discomfort”). The terms are so scientifically difficult, that the instrument actually must define the terms within the single question.
- The IUSS is poorly worded and unclear, beginning with the instruction: “After checking off each “TOILET VOID”, rate the “DEGREE OF URGENCY” you felt before making it to the toilet”. Such lack of clarity and scientific jargon continues throughout the instrument.
- The IUSS is a single-item PRO that on its face is probably not capable of capturing all the concepts and domains of the general concepts involved in this symptom/condition referred to as “urgency.” As per the draft Guidance, *“If the concept of interest is general (e.g. physical function), a single-item PRO instrument is usually unable to provide a complete understanding of the treatment’s effect because a single item cannot capture all the domains of the general concept.”*
- The IUSS lacks clarity in its confusing use of the terms “urge” and “urgency”, often in the same sentence. For example: “DEGREE OF URGENCY is meant to describe your urge to urinate.” Focus group patients noted that “urge” and “urgency” had different connotations. Several described their feelings of urinary urgency prior to having OAB as “an urge to go to the bathroom”, whereas they felt that as OAB patients they now experienced an “urgency” sensation (again, it must be emphasized that “urgency” was defined for the subjects prior to the interviews). A few participants noted that mild urgency is a misnomer. One patient said, “...but once you get the word urgency in there, I don’t consider mild an appropriate option.”
- The responses to the IUSS are confusing for several reasons, including:

- They are “*double-barreled*” in that they ask the respondent to make two separate decisions in order to pick one rating: one decision about the severity of urgency and another decision about how this feeling affects tasks. For example, “severe” (a score of 3) requires that the patient have “extreme urgency discomfort” and such “abruptly stops all activity or tasks”. This assumes that severe urgency stops all activity. In this case, a patient with severe urgency who presses on with tasks, despite severe urgency, cannot respond accurately to the question.
 - Patients with OAB are known to adjust their social and work surroundings to minimize the impact of their symptoms on activities. By doing so, it is possible to have severe urgency, yet continue with tasks (contrary to response option 3).
 - Patients with OAB can use “biofeedback” type methods to reduce the impact of their symptoms on tasks and activities.
- If any patient interviews were conducted after the initial use of the IUSS in Study IP631-003 (or, after any “pilot” study prior to Study IP631-003), documented information from such interviews could be used to improve the content and wording of a future instrument.

Construct validity: Results for the IUSS did not correlate with the clinically relevant diary measures used in current OAB trials, as hypothesized.

- In Study IP631-008, the IUSS had a “low to moderate” correlation with the average number of toilet voids per 24 hours and the average number of urge incontinence episodes per 24 hours.
- In Study IP631-008, the average volume voided did not correlate with the IUSS for the baseline or Week 12 data. According to your summary, this is “an indication that the IUSS does not access this information.”
- In Study IP631-005, the mean volume voided actually increased as the IUSS urgency severity score increased. This finding is in conflict with an expected increase in storage capacity of the bladder with reduction in urgency severity.

Additional Discussion: The Sponsor noted that change in volume recorded correlated with IUSS severity. The Sponsor may submit these data for review as part of a response, if they deem appropriate.

- In your summary on construct validity, you stated: “In certain circumstances, it is known that patient reported outcomes may not correlate highly with clinical measures, and this has been demonstrated here.”
- Finally, the IUSS attempts to exclude those voiding episodes associated with wetting or leakage (only measuring “toilet voids”). Since incontinence episodes are the current gold standard for clinical relevance, it may not be possible to compare the IUSS to the gold standard for clinical relevance.

Known-Groups Validity: Known-Groups validity is intended to show that an instrument can distinguish between two or more populations with “known” characteristics by examining scores from patients known to be different. The IUSS was not tested in “known” groups – groups with known and clear differences.

- The IUSS was not tested in normal patients - those with no known voiding problems. We believe that a normal population would have been the optimal “known group.”
- You purport known-groups validity for the IUSS for groups that are difficult to interpret and not clearly “different,” or “known,” per se.

Test-Retest Reliability: Test-retest reliability was not shown for the pre-determined Days 1 and 7 in psychometric testing of the IUSS.

- The test-retest reliability was only “moderate” (0.66 Pearson’s correlation coefficient) when comparing the average IUSS from baseline day 1 with baseline day 7. Your report states: “The desired level of reliability is usually 0.80.” Further: “Random error is the most common cause for diminished questionnaire reliability, caused by poorly worded or presented questions leading to inaccurate answers or responses that cannot be interpreted.”
 - Your subsequent analysis comparing days 2 and Day 5 does not alleviate the concern related to lack of test-retest reliability for Days 1 and 7.
- C. Do the findings of the qualitative evaluation of the IUSS, as presented in the report from Study IP631-017, support the validity of this tool as an endpoint for outcome in a clinical trial?

Division Response: No. The qualitative evaluation of the IUSS does not support its validity, based upon the deficiencies stated in our response to Question B. In addition, we note:

- There was a clear difference in responses between the two demographic focus groups (i.e., one held in Bethesda, the other in San Francisco). For example, the percentage of patients who reported either “moderate” or “severe” urgency severity was 0%-17% in the Bethesda groups, versus 80-100% in the S.F. groups. The reason for this marked difference in urgency severity needs to be clarified and taken into consideration when generating items for any subsequent PRO instrument for OAB.
- A large proportion (41%) of the focus group participants felt that a wetting accident exceeded a severe urgency episode in terms of clinical importance. This data has implications for the theory that urgency is the critical symptom in OAB. Perhaps additional focus groups are necessary to truly understand the relative clinical importance of incontinence, frequency, and urgency to OAB patients.

D. Is the Indevus Urgency Severity Scale a valid endpoint for outcome in a clinical trial?

Division Response: No.

E. Can data obtained from OAB patients using the Indevus Urgency Severity Scale be submitted to and reviewed by the Division of Reproductive and Urologic Products in support of _____ as part of the NDA for Sanctura XR)?

Division Response: Yes. You may submit this data for review. However, we caution you that the deficiencies and concerns stated in our response to Question B will be a review issue.

Discussion: *The above responses were discussed in detail. The Sponsor stated that they will take the Division's concerns and recommendations under consideration, and will consider whether to a) submit additional supportive information to justify their position(s) on the validity of the IUSS; b) work with the Division to develop an alternative PRO tool; or c) _____*

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

/s/

Mark S. Hirsch
4/27/2006 04:51:06 PM



Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION III

FACSIMILE TRANSMITTAL SHEET

DATE: August 31, 2005

To: John Berryman, Vice President, Regulatory Affairs	From: Jean Makie, Regulatory Health Project Manager
Company: Indevus Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (781) 761-0451	Fax number: (301) 827-4267
Phone number: (781) 402-3451	Phone number: (301) 827-4260
Subject: IND 71,305: August 1, 2005 EOP-2 Meeting Minutes are attached	

Total no. of pages including cover:

NOTE:

Document to be mailed:

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-4260. Thank you.

Meeting Minutes

IND: 71,305 **Type B:** EOP2 Meeting

Drug: Trospium chloride, modified release formulation

Sponsor: Indevus Pharmaceuticals

Date: August 1, 2005 **Time:** 10:30 AM – 12 PM

Location: Parklawn Building, Chesapeake Conference Room

FDA Attendees:

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)

Suresh Kaul, M.D., Medical Officer, DRUDP

Laurie McLeod-Flynn, Ph.D., Pharmacology/Toxicology Reviewer, DRUDP

Lynnda Reid, Ph.D., Supervisory Pharmacology/Toxicology DRUDP

Sarah Pope, Ph.D, Chemistry Reviewer, DRUDP

Moo Jong Rhee, Ph.D., Chemistry Team Leader, DRUDP

Sandhya Apparaju, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Doanh Tran, R.Ph., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer

Ameeta Parekh, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, DRUDP

Kate Meaker, Ph.D., Biostatistics Reviewer, DRUDP

Jean Makie, M.S., R.D, Project Manager, DRUDP

Industry Attendees

From Indevus Pharmaceuticals, Inc.

Bobby W. Sandage, Jr., Ph.D., Executive Vice President, R & D

James Shipley, M.D., Senior Vice President, Clinical Development & Medical Affairs

Ute Schwiderski, Ph.D., Vice President, Biostatistics and Data Management

Mark Harnett, M.S., Senior Director, Biostatistics and Data Management

Laura Koller, M.S., Senior Clinical Project Manager

John Berryman, M.S., Vice President, Regulatory Affairs

From Esprit Pharma (Co-Marketing Partner)

Ernest S. Biczak, M.D., Executive Vice President, Medical Affairs

Richard Brown, M.D., Vice President, Regulatory Affairs

Graham May, M.D., Consultant

Background: The Sponsor requested this Type B, End-of-Phase 2 (EOP-2) meeting on May 27, 2005. On June 30, 2005, the Sponsor submitted the following questions in their briefing package to the Division. The Division's preliminary draft responses were faxed to the Sponsor on July 29, 2005. Additional discussion held during the meeting is also summarized below under "Sponsor Response," and/or "Division Comments."

SPONSOR'S QUESTIONS:

Question 1: The SANCTURA XR NDA will contain safety and efficacy data on patients with overactive bladder from two placebo-controlled clinical studies. The first study is a two-week Phase 2 study (IP631-016) of 148 patients and the second study is the planned 12-week Phase 3 study (IP631-018) enrolling approximately 800 patients.

The SANCTURA BID (Immediate Release) NDA (21-595), which was approved by the Division on May 28, 2004, is the immediate-release formulation of trospium chloride that is currently being marketed in the U.S. NDA 21-595 contained data from over 30 studies, including two adequate and well-controlled 12-week studies with 1181 patients with overactive bladder. This data was submitted in the SANCTURA BID NDA and demonstrated the safety and efficacy of the trospium chloride immediate release formulation.

Assuming positive results in the planned Phase 3 SANCTURA XR study (IP631-018) and by referencing the Agency's Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products." (May 1998). Indevus believes that by combining the results of the planned Phase 3 study (IP631-018) and the just-completed Phase 2 study (IP631-016), along with the data generated from the SANCTURA BID NDA (21-595), will be adequate to form the basis of approval for the SANCTURA XR NDA.

Does the Division concur that the combination of data from the Phase 2 and 3 trials as outlined in the enclosed briefing package along with the data from NDA 21-595 provide adequate data to support approval of SANCTURA XR?

Division Response: No. Two Phase 3 studies are recommended to support efficacy for this indication. As in previous registration trials for the overactive bladder (OAB) indication, the sample sizes for each study may be smaller than that proposed for Protocol IP631-018. Although a single Phase 3 study with confirmatory evidence would be adequate to support the filing of an NDA submission, it may not provide sufficient evidence for approval. If you pursue this course, the single Phase 3 study should follow the Guidance to Industry entitled, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (May 1998)."

Sponsor Response: The Sponsor agreed to conduct two Phase 3 trials. The Sponsor asked the Division if it would be acceptable to conduct two similarly designed trials.

Division Response: The Division agreed this would be acceptable. The Division suggested that the Sponsor submit the Phase 3 protocols as Special Protocol Assessment requests. Reviews will be completed and comments will be provided within 45 days.

Question 2: Currently Indevus has long term safety data for approximately 1000 patients treated for 6 months and approximately 300 treated for one year.

Long term safety data on approximately 450 of the total patients (6 month and 1 year) were submitted in NDA 21-595 and total data on approximately 550 additional patients will be submitted to the Division in the Annual Report for NDA 21-595.

Assuming comparable trospium plasma levels, although not identical, between SANCTURA XR and SANCTURA BID, and comparable safety profiles for the two formulations following 12 weeks of exposure, Indevus believes that the planned Phase 3 program for SANCTURA XR along with the existing long-term safety data contained in NDA 21-595 are sufficient to demonstrate that SANCTURA XR may be approved for the indication of overactive bladder.

Indevus will also conduct a 9-month open-label extension of the planned Phase 3 study to provide additional safety information as an amendment to the pending NDA once they are available.

Does the Division concur that the planned Phase 3 safety data along with the long term safety data in NDA 21-595 are sufficient to support the indication of overactive bladder?

Division Response: No. We recommend that the original NDA submission contain safety information for at least 300 patients treated for ≥ 6 months with SANCTURA XR. Further, we request that safety data for at least 100 subjects treated for ≥ 12 months with SANCTURA XR be submitted in the 4-month Safety Update.

If plasma levels for trospium and major trospium metabolites for SANCTURA XR are similar to or lower than those for SANCTURA BID, the existing safety data contained in NDA 21-595 would provide additional support for the SANCTURA XR NDA. Otherwise, the applicability of existing safety data from NDA 21-595 will be a review issue.

Sponsor Response: The Sponsor agreed to revise the protocols accordingly. The Sponsor also stated that additional population pharmacokinetics will be completed on 250 subjects and that all data will be provided in the original NDA submission.

Division Comment: The Division recommended that geriatric subjects be included in the sparse sampling cohort so that data will be available to determine whether

Sanctura XR is no worse than the approved Sanctura in terms of adverse gastrointestinal side effects (e.g., abdominal distension and constipation) in that population.

The Division also informed the Sponsor that there are potential concerns with the excipient _____ Based on a literature review, cases of fibrosing colonopathy have been reported to be possibly related to similar excipients. Copies of abstracts can be provided. The Division asked the Sponsor if _____ has been characterized in nonclinical studies.

Sponsor Response: The Sponsor agreed to include geriatric subjects in the sparse sampling substudy. The enrollment will be capped at age at ≤ 80 years old and it is expected that 10-15% of subjects enrolled in the two trials will be ≥ 75 years old.

The Sponsor stated that the proposed _____, has been similarly used in approved products: _____. Although the _____ are not exact _____ is a common excipient. The Sponsor will confer with _____ on the nonclinical characterization of _____ and will submit details for the Division's review.

Division Comment: The Division stated that because these fibrosing colonopathy cases were reported with \geq six month use of therapy, submission of the extended 12-month safety data from the 100 patients may need to be included in the original NDA submission. Final decision remains dependent on the information provided by the Sponsor specifically for _____

Question 3: Based upon feedback from the Division at the March 11, 2005 teleconference, Indevus proposes to conduct a food effect and antacid drug interaction study (IP631-019). One arm of IP631-019 will quantitate the food effect observed with SANCTURA XR. Another arm will assess whether the co-administration of an antacid affects the pharmacokinetic profile of SANCTURA XR.

The results of this study will be used to support information for the product label regarding dosing on an empty stomach as well as aid in describing the potential drug interaction with antacids.

Does the Division concur that information from this study will be sufficient to describe the food effect and antacid drug interaction information in the product label for SANCTURA XR?

Division Response: Yes, we concur. We recommend that the food effect study be conducted prior to Phase 3 so that proper dosing instructions are used in Phase 3 studies, and subsequently applied to the label.

Sponsor Response: The Sponsor stated that they intended to start the food-effect study immediately. They likely will not have results from this study before conducting the Phase 3 trials, but will characterize food effects in the Sanctura XR NDA. In response to

the Division's concern regarding the potential for altered release in fed vs. fasted conditions, the sponsor stated that the results of the completed phase 2 study IP631-016 in 100 patients support that the formulation performs as per expectations when dosed under fasting conditions.

Division Comment: The Division cautioned the Sponsor that, although the results of this food-effect study were not required to initiate the Phase 3 studies, they could be assuming some risk if the results prove different than those observed in the 016 study. On the other hand, if the food-effect study shows an absence of or minimal change in the systemic exposure of trospium with food, knowledge of this prior to the conduct of the phase 3 trials could minimize the need for dosing restrictions.

Question 4: Indevus proposes to conduct a study (IP631-020) to assess the definitive pharmacokinetic profile of SANCTURA XR. Information from this study will be used to describe the pharmacokinetic profile of SANCTURA XR for the product labeling. Does the Division concur that IP631-020 will be sufficient to describe the pharmacokinetic profile of SANCTURA XR for the product label?

Division Response: Yes, the Division concurs with the design of the proposed PK study. Additionally, we recommend that you obtain plasma samples on Day 1 to characterize the single dose pharmacokinetics of SANCTURA XR and also measure the major metabolite(s) of trospium chloride from the SANCTURA XR formulation.

As an alternative to measuring metabolites in the definitive PK study, the division suggested that PK samples from the completed phase 2 study 016, if available can be analyzed to verify comparability of the metabolites from Sanctura XR with that of the IR formulation.

Sponsor Response: The Sponsor agreed to revise the protocols accordingly. In addition, the Sponsor will add an additional arm to the definitive PK study IP631-020 in order to investigate the PK of the lower strength 30 mg modified release formulation of trospium in geriatric patients.

ADDITIONAL COMMENTS:

Nonclinical

It is not anticipated that additional nonclinical studies would be required to support filing an NDA; however, the Division may request additional studies if unexplained toxicity, exaggerated pharmacology, or unqualified metabolites are observed or if impurity levels exceed the qualification limits.

Division Comment: The Division reiterated that dependent on the information provided by the Sponsor specifically for _____ additional nonclinical studies may be requested.

Clinical

Regarding the Phase 3 Protocol:

1. The primary endpoint is not acceptable. We recommend changing it to the total incontinence episode frequency per day (“incontinence”) OR having co-primary endpoints of incontinence and number of toilet voids per day (“frequency”).

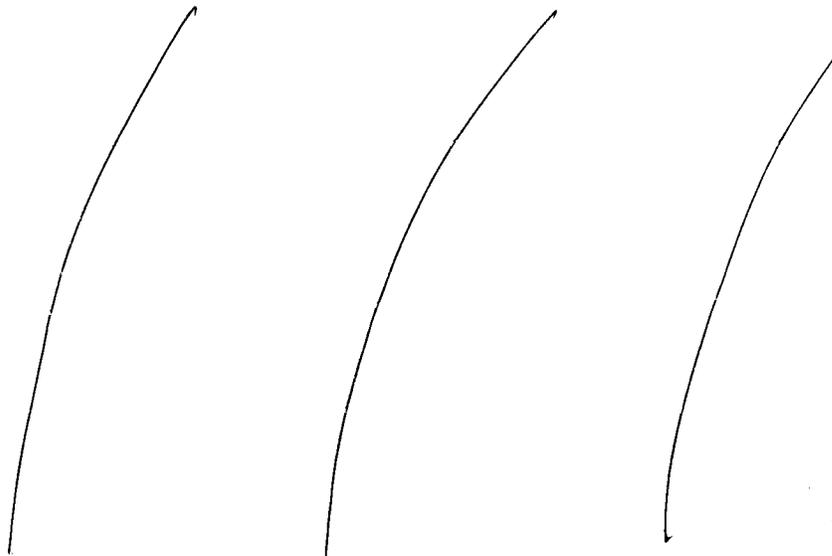
Sponsor Response: The Sponsor agreed to consider the recommendations when revising the protocols. With the conduct of two Phase 3 trials, the Sponsor asked if the Division would accept one trial with urinary frequency as a the primary endpoint and the other with incontinence as the primary endpoint.

Division Comment: The Division stated that, optimally, both trials would have both urinary frequency and incontinence as “co-primary” endpoints with each co-primary meeting at least the $p=0.5$ for statistical significance. Less than this becomes a review issue dependent on compelling evidence. The Division recommended the Sponsor include justification to support their final endpoint selection in the revised protocols.

Sponsor Response: The Sponsor agreed.

2. In subjects with serum PSA ≥ 4 ng/mL but <10 ng/mL, prostate cancer should be ruled out prior to enrollment.

Sponsor Response: The Sponsor agreed to revise the protocols accordingly.



Safety-Related Comments:

1. Propose measures to prevent dosing in the evening.

2. What is your proposed dosing recommendation for geriatric patients? In this regard, _____ Please clarify.
3. Several allergic reactions were reported in the Phase 1 studies (Subject #20 in Study 009 and Subjects #6 and #23 in Study 011). Address whether there is a relationship between allergic reactions and the new SANCTURA formulations or to dosages of trospium >20mg.
4. The incidence of abdominal distension was highest in the SANCTURA XR group in Study 011. In addition, Subject 08-6131 reported severe constipation requiring discontinuation of SANCTURA XR. Address whether abdominal distension or constipation are worse for SANCTURA XR compared to SANCTURA.

Sponsor Response: The Sponsor agreed to consider these recommendations when revising the Phase 3 protocols. Additionally, they confirmed that they would add a geriatric arm to the pharmacokinetic studies using a 30 mg dose _____ They also agreed to include a detailed discussion and characterization of any allergic reactions observed in the Phase 3 trials in the NDA submission. Dosing and administration information included in proposed labeling for Sanctura XR will be based on Phase 3 study results.

Biometrics

1. Clarify whether an interim analysis will be done on the double-blind portion of the study. If an interim analysis is planned, clarify when it will be conducted and provide justification for the need for interim analyses in this trial. Regardless of the intent of the interim analysis, we prefer that a statistical adjustment be taken for multiple looks at the data. This information must be provided in the final protocol.
2. For the efficacy analyses, specify that the Week 12 endpoint is primary.

Sponsor Response: The Sponsor agreed to provide the requisite biostatistical information.

Clinical Pharmacology & Biopharmaceutics

1. It is our understanding that the Phase 2 study IP631-016 included sparse sampling for characterizing the PK of SANCTURA XR after both morning and evening dosing regimens (protocol amendment dated January 10, 2005). We will use these results to address the diurnal variability in PK of SANCTURA XR. Please be sure to include this information in your NDA. (*Note to sponsor: Review of amendment dated July 28 currently underway*).
2. The robustness of the modified release formulation when concomitantly administered with alcoholic drinks should be considered.

Sponsor Response: The Sponsor agreed to submit the requested pharmacokinetic information in the NDA. They do not anticipate adverse effects from concomitant alcohol ingestion, but they plan to conduct in vitro dissolution

trials with different alcohols and different strengths. The Sponsor will submit results for the Division's review.

Chemistry, Manufacturing and Controls:

The following items should be addressed prior to conducting Phase 3 studies:

1. In general, CMC information for the intended Phase 3 clinical supplies (and the to-be-marketed formulation) should be established to assure the quality of the drug substance and drug product. Revisions to the quality attributes for either the drug substance or drug product, mid- or post-Phase 3, may present review issues for the NDA.
2. A specification for drug substance particle size should be established.
3. The reported change in drug substance supplier does not indicate a change in manufacturing process. If there are any changes in the manufacturing process for the drug substance, the resulting inter-site impurity profiles should be equivalent. Three commercial scale lots of drug substance manufactured at each site should be compared, and if any new impurities are noted as a result of the site or process change, they should be qualified appropriately. The drug substance lots should be equivalent in physical characteristics/properties, and all physical characterization data should be provided for review.
4. Confirmation should be provided that all primary stability and Phase 3 clinical supplies will be manufactured at the proposed commercial manufacturing site, using the manufacturing process revision outlined on page 18 (Item #3). A complete listing of all drug product batches manufactured for Phase 2 and 3 studies should be provided. This list should specify the drug substance manufacturing site, drug product batch scale, batch number, protocol number, and reference to any manufacturing information/changes for each batch.
5. Any new packaging configurations should be covered by the proposed primary stability program.
6. Bulk stability data should be provided in support of any holding times for the bulk
7. Dissolution acceptance criteria should be tightened.
8. You may wish to request a separate CMC End-of-Phase 2 meeting to further discuss these items.

Sponsor Response: The Sponsor agreed to provide the requisite CMC information.

The following items should be addressed prior to NDA submission:

1. Variations in the _____; in each capsule may affect the drug's final release profile. _____ should be considered when defining critical quality attributes and critical process controls for drug product manufacture. A step-by-step explanation of the _____ and encapsulation processes should be provided, along with the developed method of control for the resulting _____ (and therefore, the amount of API) in each capsule.
2. Due to the modified release properties of the final drug product, all rate-controlling and non-rate-controlling excipients should be identified and justified.

3. Comparative dissolution data should be submitted to support the equivalency in drug release for drug product manufactured with and without the proposed revision to sugar sphere (on page 18).
4. Complete information including specifications and supplier information should be provided for the capsules proposed for the commercial formulation. This information should be supplemented with parallel information for the previously-utilized (Phase 2) capsule shells.
5. Complete CMC information should be provided for each _____

Sponsor Response: The Sponsor agreed to provide the requisite CMC information.

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

/s/

Mark S. Hirsch
8/31/2005 11:30:29 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,305

Indevus Pharmaceuticals, Inc.
Attention: Gwyn Reis
Senior Director Regulatory Affairs
99 Hayden Avenue, Suite 200
Lexington, MA 02421

Dear Ms. Reis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for trospium chloride modified release capsules, 60 mg once daily.

We also refer to your amendment dated November 30, 2004 (serial # 000), containing Study IP631-016, entitled "A Multicenter, 2 Week, Double-Blind Study Of Trospium Chloride 60 mg QD Modified Release Capsules And Placebo Given Once Daily In The Morning Or In The Evening In Patients With Overactive Bladder."

We have completed the clinical pharmacology review of your submission and have the following comments and recommendations. Additional comments may be forwarded as we continue the reviews by other disciplines.

1. Conduct a food effect study early in development (i.e., before a Phase 3 trial) to assess the integrity of the formulation and to provide support for meal instructions in later trials.
2. Although not required, consider developing an IVIVC. For applications development and validation, please refer to FDA Guidance: "*SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation*" presently located at: <http://www.fda.gov/cder/guidance/1214fnl.pdf>
3. The pivotal clinical trial formulation should be identical to the to-be-marketed formulation. If not, appropriate bridging studies should be conducted.
4. Because the release from the modified release formulation is pH dependent, we recommend that you consider drug interactions studies for drugs that may interfere with the release of trospium chloride (e.g., antacids, anticholinergics).
5. When submitting an NDA for this formulation, provide the details on dose-finding and

the mechanism of release for both modified release components.

6. Characterize the effect of demographics (e.g., race, gender, etc.) and drug-drug interactions on the pharmacokinetics of the product. This may be accomplished via the appropriate design and analysis of Phase 2/3 studies.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Jean Makie, Sr. 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

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

/s/

Margaret Kober
3/11/05 03:42:04 PM
Chief, Project Management Staff



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 11, 2005

To: Gwyn Reis

From: Jean Makie

Company: Indevus Pharmaceuticals, Inc.

Division of Division of Reproductive
and Urologic Drug Products

Fax number: 781-861-3830

Fax number: 301-827-4267

Phone number: 781-861-8444

Phone number: 301-827-4260

Subject: December 23, 2004 teleconference minutes

Total no. of pages including cover:

Comments:

Document to be mailed:

YES

NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-4260. Thank you.

**Division of Reproductive and Urologic Drug Products
Industry Teleconference Meeting Minutes**

Date: December 23, 2004 **Time:** 1:15 – 2:15 PM

IND: 71,305 **Drug:** Trosipium chloride (extended release, once daily)

Sponsor: Indevus Pharmaceuticals, Inc.

Indication: Treatment of overactive bladder

Type of Meeting: Guidance teleconference

FDA Attendees:

Meeting Chair: Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP)

Suresh Kaul, Medical Reviewer, DRUDP

Ameeta Parekh, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader,

Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP

Leslie Kenna, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, OCPB @

DRUDP

Meeting Recorder: Jean Makie, M.S., R.D., Sr. Project Manager, DRUDP

Sponsor Attendees:

Bobby W. Sandage, Ph.D., Jr., EVP Research and Development

James Shipley, MD, SVP, Clinical Development and Medical Affairs

LuAnn Sabounjian, R.N., Executive Director, Clinical Research

Gwyn Reis, Senior Director, Regulatory Affairs

Laura Koller, Clinical Project Manager

Mark Harnett, Senior Director, Biostatistics and Data Management

Greg Lerch, VP, Regulatory Affairs and Pharmaceutical Sciences

Ute Schwiderski, Ph.D., VP, Biostatistics and Data Management

Grayson Moore, Clinical Research Associate

Rajesh Mahey, Director Manufacturing

Background: The Division requested this teleconference to discuss the Sponsor's November 2, 2004 submission (Serial #000) to IND 71,305. This submission contains Study IP631-016, entitled "A Multicenter, 2 Week, Double-Blind Study Of Trosipium Chloride 60 mg QD Modified Release Capsules And Placebo Given Once Daily In The Morning Or In The Evening In Patients With Overactive Bladder."

Issues Discussed: The Division informed the Sponsor that this protocol required further modification to ensure the safety of patients participating in this study. The following recommendations were made:

1. Modification of inclusion/exclusion criteria so that:
 - a. Only patients between the ages of 18 and 65 years will be eligible for inclusion (versus 18 and 80 years as previously specified.)
 - b. Patients with clinically significant cardiovascular disease, including history of cardiac ischemia or stroke within the past six months, cardiac conduction abnormalities on ECG, or arrhythmias will not be eligible for study inclusion.
 - c. Patients with baseline values of serum creatinine values of ≥ 1.5 mg/dL will not be eligible for inclusion in the study.
 - d. Patients with chronic constipation, defined as less than two bowel movements per week will not be eligible for study inclusion.
2. Addition of antimuscarinic-class statement to the patient informed consent document instructing patients to exercise caution while driving or operating hazardous machinery. This statement would provide consistency with current approved labeling for Sanctura™ (trospium chloride, 20 mg, twice daily).
3. Revision of the study visit schedule to include one additional office visit on Day 8 and two additional telephone calls by sites to patients on Days 3 and 11 to inquire about the patients' health status. If medically indicated, patients will be asked to return to the office for an additional visit. [Due to the addition of these health-status calls, information previously scheduled to be communicated on Days 5 and 12 to patients regarding urinary diaries will now be communicated to the patients on Days 3 and 11.] During the Day 8 visit, sites will be instructed to collect vital signs, post-void residual urines, blood to evaluate for BUN and creatinine, in addition to collecting information regarding adverse events and concomitant medications. ECGs will be performed if medically indicated.
4. Addition of study discontinuation criteria for individual patients. Any patient who experiences one of the following events will be discontinued from the study:
 - a. Seated heart-rate increases from baseline of ____ BPM. [The specific value will be specified after the Sponsor evaluates data from previous studies.]
 - b. Post-void residual urines > 200 mL.
 - c. Severe constipation defined as < 2 bowel movements per week.
 - d. Chest pain considered to be cardiac in origin.
 - e. Severe abdominal pain or distention.
5. Revision of dosing instructions regarding timing of meals relative to study medication ingestion for morning-dosing patients to mirror instructions given to evening-dosing patients.
6. Addition of sparse blood-sample collection to provide for pharmacokinetic evaluation of the new formulation.

The Sponsor agreed to amend the protocol to incorporate all of the above recommendations made by the Division.

Action Items:

1. The Sponsor will submit a letter before the 30-day safety date (December 30, 2004) committing to changing the protocol according to the verbal agreements made.
2. The Sponsor will submit a revised protocol for review by the Division.
3. The Division will provide minutes of this teleconference.

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

/s/

Mark S. Hirsch
3/11/05 01:01:41 PM