

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205383Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA #: 205383

SUPPL #

HFD #

Trade Name: Oraltag™

Generic Name: Iohexol (for oral solution)

Applicant Name: Interpharma Praha, a.s

Agent for Applicant: Otsuka Pharmaceutical Development & Commercialization

Approval Date, If Known: March 26, 2015

### 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)(2)

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:

**Oraltag is a radiographic contrast agent for use in opacification of the gastrointestinal tract during computed tomography of the abdomen and pelvis**

d) Did the applicant request exclusivity?

YES  NO

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

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).

Omnipaque (iohexol)

NDA# 18956

NDA# 20608

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:

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



YES   
Explain:

! NO   
! Explain:

Investigation #2

!  
!

YES   
Explain:

! NO   
! 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: Harris Orzach, M.D.  
Title: Clinical reviewer  
Date: March 9, 2015

Name of Office/Division Director signing form: Libero Marzella M.D., Ph.D.  
Title: Director Division of Medical Imaging Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THUY M NGUYEN  
03/26/2015

LIBERO L MARZELLA  
03/26/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205383 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
<b>Proprietary Name:</b> Oraltag <b>Established/Proper Name:</b> Oraltag (Iohexol) <b>Dosage Form:</b> Oral Solution		<b>Applicant:</b> Interpharma Praha, a.s <b>Agent for Applicant:</b> Otsuka Pharmaceutical Development & Commercialization
<b>RPM:</b> Thuy M. Nguyen		<b>Division:</b> Medical Imaging Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 02/04/15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>March 26, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None    CR – 01/08/14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 3  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	CR – 01/08/14 Approval – 03/26/15
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
• Most recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input checked="" type="checkbox"/> Included 03/25/15
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 09/26/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling ( <i>if it is division-proposed labeling, it should be in track-changes format</i> )	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
• Most-recent draft labeling (applicant)	<input checked="" type="checkbox"/> 03/26/15
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) ( <i>indicate date(s)</i> )	12/19/14 12/17/14
• Review(s) ( <i>indicate date(s)</i> )	
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input checked="" type="checkbox"/> 01/07/14 DMEPA: <input checked="" type="checkbox"/> 12/16/14 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 03/03/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> PT review: 02/25/15 Other: DPMH, 03/16/15
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	01/07/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 02/04/15
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included 03/26/15
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>11/13/13</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	Enclosed
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 03/20/12 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A <input type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 03/25/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	02/27/15 Concurrence – 02/27/15 02/27/15 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	03/17/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	N/A N/A <input checked="" type="checkbox"/> None N/A
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	Concurrence – 03/02/15
Statistical Review(s) ( <i>indicate date for each review</i> )	03/02/15
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	Concurrence – 02/25/15
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	02/25/15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	10/09/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	02/25/15 12/05/13
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	04/24/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	CMC Review, 11/01/13
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection:	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 12/03/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications:                             <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ For Breakthrough Therapy(BT) Designated drugs:                             <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> N/A ( <i>Send email to CDER OND IO</i> )
<ul style="list-style-type: none"> <li>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure Pediatric Record is accurate</li> </ul>	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send approval email within one business day to CDER-APPROVALS</li> </ul>	<input checked="" type="checkbox"/> Done

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/s/  
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THUY M NGUYEN  
03/27/2015

**From:** [Kadash, Marjory](#)  
**To:** [Nguyen, Thuy M](#)  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Label Request - 03/26/15 / re: Spon's Labels email dated 03/20/15 / re: submission date, 09/26/14  
**Date:** Thursday, March 26, 2015 12:19:28 PM

---

Hi Thuy,

I have decided against using another representative; I will wait for any additional requests and handle them directly.

Thank you.

**Marjory Kadash**  
Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
508 Carnegie Center Drive  
Princeton, New Jersey 08540

Office: 609.524.6876  
Cell: (b) (6)  
Fax: 240.514.3976  
Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Nguyen, Thuy M [mailto:[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)]  
**Sent:** Thursday, March 26, 2015 12:17 PM  
**To:** Kadash, Marjory  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Label Request - 03/26/15 / re: Spon's Labels email dated 03/20/15 / re: submission date, 09/26/14

Dear Ms. Kadash,

Per your voice mail, 03/26/15, if there is another Sponsor's authorized representative, please include the person on the email response to the FDA regarding the revised labels.

Thank you.

Sincerely,  
Thuy M. Nguyen

---

**From:** Nguyen, Thuy M  
**Sent:** Thursday, March 26, 2015 12:06 PM  
**To:** [Marjory.Kadash@otsuka-us.com](mailto:Marjory.Kadash@otsuka-us.com)  
**Subject:** Ms. Kadash: NDA 205383 (Oraltag): FDA Label Request - 03/26/15 / re: Spon's Labels email dated 03/20/15 / re: submission date, 09/26/14

Dear Ms. Kadash (for Sponsor: Interpharma Praha, a.s.)

Regarding NDA 205383: Oraltag (Iohexol), submission dated September 26, 2014, and the Sponsor's labels received by email on March 20, 2015, below are the **FDA Label Comments and Request - March 26, 2015:**

**For the entire bottle, foil pouch and carton labels, please revise (replace), as follows:**

(b) (4) **bound iodine” TO “carbon bound iodine”.**

Please provide the revised labels (in PDF) as an annotated version (with red-lined, track-changes) along with a clean revised version.

By 1:00 pm, EST, today – March 26, 2015 in the interest of time, first provide the revised labels via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and then follow up with a formal official submission to the U.S. FDA CDER - Division of Medical Imaging Products via ESG / Gateway electronic submission.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Office: (301) 796-1427  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

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/s/  
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THUY M NGUYEN  
03/26/2015

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: Ms. Marjory Kadash (for Sponsor: Interpharma Praha, a.s.)  
Otsuka Pharmaceutical Development & Commercialization  
Office: (609) 524-6876 / Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)**

**Regarding NDA 205383: Oraltag™ (Iohexol), submission dated September 26, 2014, the FDA has the following Labeling Revisions, Comments & Request – March 25, 2015.**

**Please review the attached FDA labeling in its entirety.**

**And provide the revised labeling (in MS Word) as an annotated version (with red-lined, track-changes) along with a clean revised version.**

**By 10:00 am, EST, Thursday - March 26, 2015, in the interest of time, first provide the revised labeling via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and then follow up with a formal official submission to the U.S. FDA CDER - Division of Medical Imaging Products via ESG / Gateway electronic submission.**

**If you have any questions, please contact me.**

**Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Office: (301) 796-1427  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)**

**NDA 205383: Oraltag™ (Iohexol)**

**FDA Labeling Revisions & Comments – See DRAFT labeling (below): March 25, 2015**

6 Pages of Draft Labeling have been Withheld  
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/s/  
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THUY M NGUYEN  
03/25/2015

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: Ms. Marjory Kadash (for Sponsor: Interpharma Praha, a.s.)  
Otsuka Pharmaceutical Development & Commercialization  
Office: (609) 524-6876 / Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)**

**Regarding NDA 205383: Oraltag™ (Iohexol), submission dated September 26, 2014, the FDA has the following Labeling Revisions, Comments & Request – March 24, 2015.**

**Please review the attached FDA labeling in its entirety.**

**And provide the revised labeling (in MS Word) as an annotated version (with red-lined, track-changes) along with a clean revised version.**

**By 9:00 am, EST, Wednesday – March 25, 2015, in the interest of time, first provide the revised labeling via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and then follow up with a formal official submission to the U.S. FDA CDER - Division of Medical Imaging Products via ESG / Gateway electronic submission.**

**If you have any questions, please contact me.**

**Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Office: (301) 796-1427  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)**

**NDA 205383: Oraltag™ (Iohexol)**

**FDA Labeling Revisions & Comments – See DRAFT labeling (below): March 24, 2015**

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/s/  
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THUY M NGUYEN  
03/24/2015

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: Ms. Marjory Kadash (for Sponsor: Interpharma Praha, a.s.)  
Otsuka Pharmaceutical Development & Commercialization  
Office: (609) 524-6876 / Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)**

**Regarding NDA 205383: Oraltag™ (Iohexol), submission dated September 26, 2014, the FDA has the following Labeling Revisions, Comments & Request – March 20, 2015.**

**Please review the attached FDA labeling in its entirety.**

**And provide the revised labeling (in MS Word) as an annotated version (with red-lined, track-changes) along with a clean revised version.**

**By 9:00 am, EST, Monday – March 23, 2015, in the interest of time, first provide the revised labeling via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and then follow up with a formal official submission to the U.S. FDA CDER - Division of Medical Imaging Products via ESG / Gateway electronic submission.**

**If you have any questions, please contact me.**

**Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Office: (301) 796-1427  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)**

**NDA 205383: Oraltag™ (Iohexol)**

**FDA Labeling Revisions & Comments – See draft labeling (below): March 20, 2015**

6 Pages of Draft Labeling have been  
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/s/  
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THUY M NGUYEN  
03/20/2015

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

**TO: Ms. Marjory Kadash (for Sponsor: Interpharma Praha, a.s.)  
Otsuka Pharmaceutical Development & Commercialization  
Office: (609) 524-6876 / Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)**

**Regarding NDA 205383: Oraltag™ (Iohexol), submission dated September 26, 2014, the FDA has the following Labeling and Label Comments & Request – March 12, 2015.**

**Please provide the revised labeling (in MS Word) and revised labels (in PDF) as an annotated version (with red-lined, track-changes) along with a clean revised version.**

**By 9:00 am, EST, Monday – March 16, 2015, in the interest of time, first provide the revised labeling and labels via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and then follow up with a formal official submission to the U.S. FDA CDER - Division of Medical Imaging Products via ESG / Gateway electronic submission.**

**If you have any questions, please contact me.**

**Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Office: (301) 796-1427  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)**

**NDA 205383: Oraltag™ (Iohexol)**

**FDA Label Request – March 12, 2015**

**LABELS (Bottle, Foil Pouch and Carton)**

**Revise the labels, as follows:**

**BOTTLE**

- remove [REDACTED] (b) (4).
- add strength
- add statement to protect Oraltag solutions during storage

example,

**Oraltag™  
(iohexol)  
for oral solution**

9.7 g of iohexol powder  
(equivalent to 4.5 g [REDACTED] (b) (4) bound iodine)

Protect prepared solutions of Oraltag from strong daylight and direct exposure to sunlight.

**FOIL POUCH**

- remove [REDACTED] (b) (4).
- add equivalent amount of [REDACTED] (b) (4) bound iodine to the strength statement.

example,

**Oraltag™  
(iohexol) for oral solution**

Contains a single-use bottle with  
9.7 g of iohexol powder  
(equivalent to 4.5 g [REDACTED] (b) (4) bound iodine)

**CARTON**

- remove [REDACTED] (b) (4).
- add strength

example,

**Oraltag™  
(iohexol) for oral solution**

9.7 g of iohexol powder  
(equivalent to 4.5 g [REDACTED] (b) (4) bound iodine)

**NDA 205383: Oraltag™ (Iohexol)**

**FDA Labeling Comments – See draft labeling (below): March 12, 2015**

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THUY M NGUYEN  
03/12/2015

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING  
PRODUCTS (DMIP)**

**INTERNAL TEAM AND LABELING MEETINGS MINUTES**

**NDA:** 205383

**DRUG NAME:** Oraltag™ (Iohexol) for Oral Solution

**SPONSOR:** Interpharma Praha, a.s

**SUBMISSION DATE:** September 26, 2014

**MEETING DATES:** February 3, 10 and 23, 2015

**AGENDA:** The review team met to discuss the review status and labeling. The Project Manager reminded the team of the primary and secondary review due date of February 27, 2015.

**Meeting Minutes Recorded By: T.Nguyen, DMIP**

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THUY M NGUYEN  
03/09/2015

**From:** Nguyen, Thuy M  
**To:** [Salazar Driver, Milagros](#); [Leutzinger, Eldon E](#); [Christodoulou, Danae D](#); [McKnight, Rebecca](#); [Marzella, Libero](#); [Gorovets, Alex](#); [Orzach, Harris](#); [Ye, Brenda](#); [Hargus, Sally](#); [Laniyonu, Adebayo A](#); [John, Christy](#); [Williams, Gene M](#); [Cole, Jessica](#); [Riley, Bryan S](#); [Misra, Satish](#); [Zalkikar, Jyoti](#); [Gwise, Thomas E](#); [Todd, Nushin E](#); [Krefting, Ira](#); [Tyson, Rene](#)  
**Subject:** Milagros: NDA 205383 (Oraltag): Spon's CMC Response - 02/04/15  
**Date:** Wednesday, February 04, 2015 11:55:00 AM  
**Attachments:** [RE Ms. Kadash NDA 205383 \(Oraltag\) FDA Chemistry Information Request - 020415 re submission dated 092614.msg](#)

---

Hi Milagros,

Please find attached the Spon's CMC Response – Feb 4.

Thank you,

Thuy

---

**From:** Nguyen, Thuy M  
**Sent:** Tuesday, February 03, 2015 2:17 PM  
**To:** Salazar Driver, Milagros; Leutzinger, Eldon E; Christodoulou, Danae D; McKnight, Rebecca  
**Subject:** Milagros: FW: NDA 205-383 / Oraltag / CMC IR to Spon

Hi Milagros,

Thank you.

I will forward the IR to the Spon.

-Thuy

---

**From:** Salazar Driver, Milagros  
**Sent:** Tuesday, February 03, 2015 2:15 PM  
**To:** Nguyen, Thuy M  
**Cc:** Leutzinger, Eldon E; Christodoulou, Danae D  
**Subject:** NDA 205-383

Hi Thuy,

As requested, this is the comment to the sponsor from past label reviews:

[“Provide the osmolality of Oraltag at the concentration of 21 mgI/mL.”](#)

Thanks,

Milagros

**From:** Nguyen, Thuy M  
**To:** "[Kadash, Marjory](#)"  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14  
**Date:** Wednesday, February 04, 2015 11:52:00 AM

---

Dear Ms. Kadash,

Thank you for the CMC Response, 02/04/15.

Sincerely,  
Thuy M. Nguyen

---

**From:** Kadash, Marjory [mailto:[Marjory.Kadash@otsuka-us.com](mailto:Marjory.Kadash@otsuka-us.com)]  
**Sent:** Wednesday, February 04, 2015 11:46 AM  
**To:** Nguyen, Thuy M  
**Cc:** Kadash, Marjory  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14

Dear Thuy,

We have calculated the osmolality of Oraltag at a concentration of 21 mg/mL in water. It is 55 mmol/kg.

We are available to answer any other questions your team may have.

Marjory

**Marjory Kadash**  
Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
508 Carnegie Center Drive  
Princeton, New Jersey 08540

Office: 609.524.6876  
Cell: (b) (6)  
Fax: 240.514.3976  
Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Nguyen, Thuy M [mailto:[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)]  
**Sent:** Wednesday, February 04, 2015 9:51 AM  
**To:** Kadash, Marjory  
**Subject:** Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14

Dear Ms. Kadash,

I am the Project Manager at the FDA CDER – Division of Medical Imaging Products assigned to NDA 205383 (Oraltag) since Mr. James Moore is no longer with the FDA.

Regarding NDA 205383 (Oraltag), submission dated September 26, 2014, the FDA has the following **Chemistry Information Request – February 4, 2015:**

**Provide the osmolality of Oraltag at the concentration of 21 mgI/mL.**

Please provide a response to my attention via email by 12:00 pm, EST – today, February 4, 2015.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
(301) 796-1427

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THUY M NGUYEN  
02/04/2015

**From:** Nguyen, Thuy M  
**To:** "[Kadash, Marjory](#)"  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14  
**Date:** Wednesday, February 04, 2015 11:52:00 AM

---

Dear Ms. Kadash,

Thank you for the CMC Response, 02/04/15.

Sincerely,  
Thuy M. Nguyen

---

**From:** Kadash, Marjory [<mailto:Marjory.Kadash@otsuka-us.com>]  
**Sent:** Wednesday, February 04, 2015 11:46 AM  
**To:** Nguyen, Thuy M  
**Cc:** Kadash, Marjory  
**Subject:** RE: Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14

Dear Thuy,

We have calculated the osmolality of Oraltag at a concentration of 21 mg/mL in water. It is 55 mmol/kg.

We are available to answer any other questions your team may have.

Marjory

**Marjory Kadash**  
Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
508 Carnegie Center Drive  
Princeton, New Jersey 08540

Office: 609.524.6876  
Cell: (b) (6)  
Fax: 240.514.3976  
Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Nguyen, Thuy M [<mailto:Thuy.Nguyen@fda.hhs.gov>]  
**Sent:** Wednesday, February 04, 2015 9:51 AM  
**To:** Kadash, Marjory  
**Subject:** Ms. Kadash: NDA 205383 (Oraltag): FDA Chemistry Information Request - 02/04/15 / re: submission dated 09/26/14

Dear Ms. Kadash,

I am the Project Manager at the FDA CDER – Division of Medical Imaging Products assigned to NDA 205383 (Oraltag) since Mr. James Moore is no longer with the FDA.

Regarding NDA 205383 (Oraltag), submission dated September 26, 2014, the FDA has the following **Chemistry Information Request – February 4, 2015:**

**Provide the osmolality of Oraltag at the concentration of 21 mgI/mL.**

Please provide a response to my attention via email by 12:00 pm, EST – today, February 4, 2015.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
(301) 796-1427

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THUY M NGUYEN  
02/04/2015

**From:** Ayalasonmayajula, Vasantha  
**To:** "[Kadash, Marjory](#)"  
**Cc:** [Moore, James W](#); [Flowers, Louis](#); [Jenkins, Darrell](#)  
**Subject:** RE: Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution; Sequence 0016  
**Date:** Monday, January 05, 2015 8:14:00 AM  
**Attachments:** [NDA205383 Proprietary Name Review Action.pdf](#)

---

Dear Ms.Kadash,

Wish you a Happy New Year too.

Reference is made to:

- Your correspondence, dated and received June 4, 2013, requesting review of your proposed proprietary name, Oraltag
- Your correspondence, dated and received September, 30, 2014, requesting review of your proposed proprietary name, Oraltag.
- Your amendment, dated and received December 17, 2014, updating the mailing address for the US Agent

Action has been taken by DMEPA and the action letter has been mailed to the mailing address provided in your cover letter by FDA on 12/19/2014. Attached is also a copy of the action letter for your reference. Please let me know if you have any questions.

Thanks,  
Vasantha

\*\*\*\*\*

Sincerely,  
**Vasantha Ayala**  
**Senior Regulatory Project Manager**  
**Office of Surveillance and Epidemiology | Project Management Staff**  
**Ph: 240-402-5035 (O)**  
**Email: [Vasantha.ayalasonmayajula@fda.hhs.gov](mailto:Vasantha.ayalasonmayajula@fda.hhs.gov)**

---

**From:** Kadash, Marjory [<mailto:Marjory.Kadash@otsuka-us.com>]  
**Sent:** Monday, January 05, 2015 7:51 AM  
**To:** Ayalasonmayajula, Vasantha  
**Cc:** Moore, James W; Flowers, Louis  
**Subject:** RE: Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution; Sequence 0016

Dear Vasantha,

Happy New Year!

I am following up on the action you mentioned below. We have not received a communication. Could you please let me know if something has been sent? If yes, could you please provide a copy by e-mail?

Thanks for your assistance,

Marjory

**Marjory Kadash**  
Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
508 Carnegie Center Drive  
Princeton, New Jersey 08540

Office: 609.524.6876

Cell: (b) (6)

Fax: 240.514.3976

Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Ayalasomayajula, Vasantha [<mailto:Vasantha.Ayalasomayajula@fda.hhs.gov>]  
**Sent:** Wednesday, December 17, 2014 12:17 PM  
**To:** Kadash, Marjory  
**Cc:** Moore, James W; Flowers, Louis  
**Subject:** RE: Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution; Sequence 0016

Dear Marjory,

Can you please let me know if you will be sending in the new address today? We are ready to take an action and it would be good if the submission came in today.

Thanks,

Vasantha

---

**From:** Kadash, Marjory [<mailto:Marjory.Kadash@otsuka-us.com>]  
**Sent:** Tuesday, December 16, 2014 10:14 AM  
**To:** Ayalasomayajula, Vasantha  
**Cc:** Moore, James W; Kadash, Marjory  
**Subject:** RE: Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution; Sequence 0016

Dear Vasantha,

This e-mail is in reference to NDA 205383 for Iohexol (b) (4) Oral Solution. You will recall that the NDA is under review by DMIP and we also have a pending Request for Proprietary Name Review.

I will be sending an Administrative change to the NDA tomorrow; it will be Sequence 0017. The change is simply a change in my address, as the US Agent. There are no other changes in contact information for me or any other facilities.

Please confirm that you are still the Project Manager at OSE assigned to this product so that I can copy you on the submission.

Thank you in advance for your assistance in providing this confirmation,

Marjory

**Marjory Kadash**

Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
508 Carnegie Center Drive  
Princeton, New Jersey 08540

Office: 609.524.6876

Cell: (b) (6)

Fax: 240.514.3976

Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Kadash, Marjory

**Sent:** Tuesday, September 30, 2014 2:23 PM

**To:** Ayalasomayajula, Vasantha ([Vasantha.Ayalasomayajula@fda.hhs.gov](mailto:Vasantha.Ayalasomayajula@fda.hhs.gov))

**Cc:** 'Moore, James W'

**Subject:** Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution; Sequence 0016

Dear Vasantha,

The purpose of this e-mail is to notify you that we have sent Sequence 0016 to the NDA 205383 for Iohexol (b) (4) Oral Solution through the electronic gateway today.

This submission contains the request for re-review of the proposed proprietary name as a separate submission to the NDA per your request.

Please find attached the cover letter for this new submission as well as a copy of the actual Request for Proprietary Name Review. Please note that this Request for Proprietary Name Review is identical to the one sent below as part of Sequence 0015; we have not made any changes to it.

I hope this new submission meets your needs. Please do not hesitate to contact me if you have

any questions or require additional information.

Kind regards,

Marjory

**Marjory Kadash**

Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540

Office: 609.524.6876

Cell: (b) (6)

Fax: 240.514.3976

Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

---

**From:** Kadash, Marjory

**Sent:** Friday, September 26, 2014 3:22 PM

**To:** Ayalasonmayajula, Vasantha ([Vasantha.Ayalasonmayajula@fda.hhs.gov](mailto:Vasantha.Ayalasonmayajula@fda.hhs.gov))

**Cc:** Kadash, Marjory

**Subject:** Request for Proprietary Name Review: NDA 205383: Iohexol (b) (4) Oral Solution

Dear Vasantha,

This e-mail concerns NDA 205383 for Iohexol (b) (4) Oral Solution and a request for a re-review of the conditionally accepted proprietary name Oraltag™. Please recall that I communicated with you several weeks ago about this request.

A Resubmission to the NDA, Sequence 0015, was submitted today through the FDA electronic gateway. This sequence includes the updated Request for Proprietary Name Review noted above.

Information about the submission is provided in the attached cover letter. A copy of the actual Request for Proprietary Name Review is also attached for your convenience.

Please let me know if you have any questions or require additional information. Of note, if samples of the labeled primary container, a beverage bottle, would be helpful for the reviewers, we would be happy to provide these.

Thank you in advance for your project management support,

Marjory

**Marjory Kadash**

Director, Regulatory Affairs

Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540

Office: 609.524.6876

Cell: [REDACTED] (b) (6)

Fax: 240.514.3976

Email: [marjory.kadash@otsuka-us.com](mailto:marjory.kadash@otsuka-us.com)

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/s/

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VASANTHA S AYALASOMAYAJULA  
01/08/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205383

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Interpharma Praha, a.s.  
c/o Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
508 Carnegie Center Drive  
Princeton, NJ 08540

ATTENTION: Marjory Kadash  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs

Dear Ms.Kadash:

Please refer to

- Your New Drug Application (NDA dated and received March 11, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Iohexol (b) (4) Oral Solution 9.7 grams of iohexol powder (4.5 grams of Iodine)
- Your class 2 resubmission, dated and received September 26, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for for Iohexol (b) (4) Oral Solution 9.7 grams of iohexol powder (4.5 grams of Iodine)

We also refer to:

- Your correspondence, dated and received June 4, 2013, requesting review of your proposed proprietary name, Oraltag
- Your correspondence, dated and received September, 30, 2014, requesting review of your proposed proprietary name, Oraltag.
- Your amendment, dated and received December 17, 2014, updating the mailing address for the US Agent

We have completed our review of the proposed proprietary name, Oraltag, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your September 30, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact James W. Moore, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
12/19/2014



NDA 205-383

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, NJ 08540

Dear Ms. Kadesh:

We acknowledge receipt on September 26, 2014, of your September 25, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for OralTag (Iohexol) for Oral Solution.

We consider this a complete, class 2 response to our January 10, 2014 action letter. Therefore, the user fee goal date is March 26, 2015.

If you have any questions, call me at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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JAMES W MOORE  
10/06/2014

**For Internal Use Only**

Meeting Request Withdrawn/Meeting Cancellation Form

Application Type/Number	NDA 205-383
Meeting Type/Code	Type B
<b>DATE</b> Meeting Request Withdrawn by Sponsor	
<b>DATE</b> Meeting Cancelled by Sponsor or FDA (per communication with sponsor)	August 12, 2014
<b>DATE</b> FDA-Initiated Meeting Cancelled (per communication with sponsor)	
Scheduled Meeting Date	August 13, 2014
Reason for Withdrawal/Cancellation	Otsuka stated that their questions were answered sufficiently with the Preliminary Comments provided on Friday, August 8, 2014, therefore a meeting was not necessary.
Project Manager	James Moore, PharmD., M.A.

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/s/  
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JAMES W MOORE  
08/19/2014



NDA 205-383

**MEETING PRELIMINARY COMMENTS**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, NJ 08540

Dear Ms. Kadesh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OralTag™ (Iohexol) (b) (4) Oral Solution.

We also refer to your July 3, 2014, correspondence, received July 3, 2014, requesting a meeting to discuss the planned resubmission of your New Drug Application for OralTag™.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Health Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** [Type B]  
**Meeting Category:** [Other]  
**Meeting Date and Time:** [August 13, 2014, 1:30 PM-2:30 PM]  
**Meeting Location:** [FDA White Oak Campus, Building 22, Conference Room 1313]  
**Application Number:** [205-383]  
**Product Name:** [OralTag™ (Iohexol)] (b) (4) Oral Solution  
**Indication:** [For oral administration as an opacification agent during computed tomography (CT) of the abdomen and pelvis]  
**Sponsor/Applicant Name:** [Interpharma Praha a.s., U.S. Agent-Otsuka Pharmaceuticals]

**FDA ATTENDEES (tentative)**

Libero Marzella, M.D., Ph.D., Director, DMIP  
Alex Gorovets, M.D., Acting Deputy Director, DMIP  
Brenda Ye, M.D., Clinical Team Leader, DMIP  
Ira Krefting, M.D., Deputy Director for Safety, DMIP  
Sally Hargus, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader, DMIP  
Eldon Leutzinger, Ph.D., Chemistry Lead, ONDQA  
Milagros Salazar-Driver, Ph.D., Chemistry Reviewer, ONDQA  
Danae Christodoulou, Ph.D., Branch Chief, ONDQA  
Robert Wittorf, PharmD., OC  
Mahesh Ramanadham, PharmD., OC  
Vasantha Ayalasomayajula, PharmD., Office of Safety Evaluation  
Kyong Kang, PharmD., Chief, Project Management Staff, DMIP  
Matthew Spataro, ORA  
Matthew Mouris, ORA  
James Moore, PharmD., M.A., Regulatory Health Project Manager, DMIP  
Nushin Todd, M.D., Deputy Director for Labeling, DMIP

**SPONSOR ATTENDEES**

Yosuke Maki, MS, Executive Vice President, Interpharma Praha, a.s.  
Ivan Hlvacek, Chief Operating Officer, Interpharma Praha, a.s.  
Scott Hollander, Vice President Business Development, Otsuka Novel Products, Medical Imaging  
Joel Timberlake, Vice President Manufacturing, Otsuka Novel Products, Medical Imaging  
Marjory Kadash, MS, PMP, Director, Regulatory Affairs, Otsuka Novel Products, Medical Imaging  
Yoshito Masuda, MS, RPh, Director, Eastern European Office, Otsuka Pharmaceutical Co., Ltd.  
(b) (4)



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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## **1.0 INTRODUCTION**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 13, 2014, 1:30 PM-2:30 PM, FDA White Oak Campus, Building 22, Conference Room 1313, Silver Spring, Maryland 20903 between Otsuka Pharmaceutical Development & Commercialization, Inc. and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory health project manager (RHPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RHPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## **2.0 BACKGROUND**

The purpose of this meeting is (1) to confirm that the NDA resubmission will be considered complete and will address all the deficiencies listed in the Complete Response Letter issued on January 8, 2014 (2) to assure a clear understanding of any outstanding requirement to allow the scheduling of any required pre-approval inspections (PAIs) and (3) to provide a status report of actions taken by Otsuka to prepare for the NDA Resubmission, including pre-approval inspection readiness of UltraSeal, and stability testing underway at Interpharma Praha.

Otsuka plans to resubmit their application for OralTag<sup>TM</sup> in late September or early October, 2014.

The indication proposed by Otsuka Pharmaceutical Development is the use of OralTag<sup>TM</sup> (iohexol) for oral administration as an opacification agent during computed tomography (CT) of the abdomen and pelvis.

The responses to Otsuka's questions from the meeting package are cited in the discussion section below. Otsuka's questions are italicized and FDA's responses are bolded. FDA's responses are organized by discipline/subject area.

### 3.0 DISCUSSION

#### Chemistry/Clinical/Pharmacology/Toxicology

*Otsuka's Question 1:*

*To address all issues listed in the Complete Response letter, Otsuka intends to make references to previously submitted information and also provide updated sections of the NDA. An outline of the planned NDA Resubmission is provided in Table 1.6.1-1. Does FDA agree that the references to previously submitted information together with the proposed updated sections, as outlined in Table 1.6.1-1, will be sufficient to address all elements of the Complete Response letter?*

**FDA's Response to Question 1:**

**Yes, the CMC response is acceptable with the 6 months stability on two stability lots and the results of the photostability study where both will include testing for free iodine and free iodide. Clarify whether your proposed stability lots have been manufactured on the (b) (4) intended for commercial production.**

**Regarding the Safety Update, you should provide copies of the Nonclinical and Clinical publications referenced in the update.**

#### Regulatory

*Otsuka's Question 2:*

*Otsuka plans to file the NDA Resubmission at the end of September/beginning of October 2014 when the 6-month stability data for the 2 performance qualification lots are available. Otsuka's understanding from the November 4, 2013 teleconference and from the Complete Response letter was that the PAI at Ultra Seal would be scheduled once the NYK District Office was notified that Ultra Seal was ready for inspection. Of note, we believe that the PAI can proceed independently from accruing the stability data at IPP. Please, could the FDA clarify if any additional information is needed at this time to proceed with scheduling the PAI at Ultra Seal?*

**FDA's Response to Question 2:**

**The Office of Compliance will perform a compliance evaluation for all listed facilities upon resubmission of the application to determine the need for inspection. No additional information is required at this time. Per the Sponsor, the NDA resubmission will occur at the end of September/beginning of October 2014. The agency appreciates notification of inspectional readiness from firms; however, additional factors are used in determining a firm's compliance status. These factors include, but are not limited to, the firm's cGMP compliance, inspectional history, and manufacturing data submitted in the application.**

*Otsuka's Question 3:*

*Please confirm that Final Printed Labeling (in SPL format) should not be included in the Resubmission but should be submitted subsequently, at the time of approval.*

**FDA's Response to Question 3:**

**Since the package insert will undergo some revisions during the review process, it is not necessary to submit the SPL when the application is resubmitted. However, a draft package insert, revised draft labeling for the container, the foil pouch, and the carton must accompany your resubmission.**

**In addition to the labeling that must accompany your resubmitted application; you must submit under separate cover, a request for a Proprietary Name review by the Office of Surveillance and Epidemiology at the time of resubmission of your OralTag™ application.**

*Otsuka's Question 4:*

*Please would the Agency outline the steps anticipated following the NDA Resubmission.*

**FDA's Response to Question 4:**

**The process will be similar to the process employed during the first review cycle for your application. An acknowledgement letter will be sent to Otsuka noting receipt of the resubmission. CFR 21 314.110(4)(b)(1)(i)(ii) describes how resubmissions are designated by the Agency and the time allocated for the review of each.**

**Subsequent to the issue of the acknowledgement letter, additional information may be requested to complete the review of your submission. If additional information is needed, you will be contacted by the Division. After the review of the submitted material is complete and if it is acceptable, draft labeling will be provided for Otsuka's review and concurrence.**

**Concurrent with this review by the Division, the inspection of designated facilities will be scheduled and conducted by the Office of Compliance and FDA's field office(s).**

**4.0 PREA REQUIREMENTS**

**Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.**

**Since you have fulfilled this requirement for pediatric studies, no additional pediatric studies are required.**

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/s/  
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JAMES W MOORE  
08/11/2014



NDA 205-383

**MEETING REQUEST GRANTED**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, NJ 08540

Dear Ms. Kadesh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OralTag (Iohexol) (b) (4) Oral Solution.

We also refer to your July 3, 2014, correspondence requesting a Type A meeting to discuss (1) whether the planned NDA Resubmission will be considered complete and address all the deficiencies listed in the Complete Response letter dated January 8, 2014 and received January 10, 2014, (2) assure that Otsuka has a clear understanding of any outstanding requirements that may delay the scheduling of any required pre-approval inspections (PAIs), and (3) provide a status report of actions taken by Otsuka to prepare for the NDA Resubmission, including pre-approval inspection-readiness of Ultra Seal, and stability testing underway at Interpharma Praha.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

**Date:** August 13, 2014  
**Time:** 1:30 PM-2:30 PM  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1313  
Silver Spring, Maryland 20903

**Invited CDER Participants:** Libero Marzella, M.D., Ph.D., Director, DMIP  
Alex Gorovets, M.D. Acting Deputy Director, DMIP  
Ira Krefting, M.D, Deputy Director for Safety, DMIP  
Sally Hargus, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader, DMIP  
Kyong Kang, PharmD., Chief Project Management Staff, DMIP  
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP  
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, OCP  
Tien Mien Chen, Ph.D., Biopharmaceutics Reviewer, OPS  
Milagros Salazar-Driver, Ph.D., Chemistry Reviewer, ONDQA  
Eldon Leutzinger, Ph.D., Chemistry Lead, ONDQA  
James Moore, PharmD., M.A., Regulatory Health Project Manager, DMIP  
Robert Wittorf, PharmD., OC  
Mahesh Ramanadham, PharmD., OC

Please e-mail me any updates to your attendees at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access. A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: James Moore (301) 796-1986.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 12 desk copies to me) at least 1 month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by July 14, 2014, we may cancel or reschedule the meeting.

Submit the 12 desk copies to the following address:

James Moore, PharmD., M.A.  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5435  
10903 New Hampshire Avenue  
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

Please be advised that if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Include in your meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

If you have any questions, call me at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD, M.A.  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure:  
Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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JAMES W MOORE  
07/07/2014



NDA 205-383

**GENERAL ADVICE**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, NJ 08540

Dear Ms. Kadesh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iohexol (b) (4) Oral Solution.

We refer to your May 15, 2014, submission, which contained a status update regarding the inspection-readiness of the manufacturing facility for Ultra Seal, and notification of your planned resubmission in October, 2014. In your May 15, 2014 correspondence, you notified FDA that the resubmission will contain the 6-month stability data requested by FDA in the CR letter of January 10, 2014.

We have reviewed the referenced material and have the following comments.

1. The review clock for this application will not begin until your application has been resubmitted and all deficiencies contained in the CR letter have been addressed including the six month stability data. Once the resubmission is provided to FDA, an evaluation of manufacturing facilities supporting the application will be conducted as part of the review process.

If you have any questions, call James Moore, Regulatory Health Project Manager, at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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JAMES W MOORE  
06/19/2014

ALEXANDER GOROVETS  
06/19/2014



NDA 205-383

**INFORMATION REQUEST**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
Director, Regulatory Affairs  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540

Dear Ms. Kadesh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OralTag™ (Iohexol) for Oral Solution.

We also refer to your March 11, 2013 original NDA submission, containing the product labeling for this product.

We are reviewing the product labeling section of your submission and have the following comments and information requests.

1. Remove the abbreviations (e.g., gI, mgI, CLL, SLL) and replace them with this information spelled out (e.g., grams of Iodine, milligrams of Iodine, etc).
2. In order to facilitate a more clinically meaningful presentation of the dose to be administered, [REDACTED] (b) (4) please clarify how the product is being currently administered in practice and use such a clarification for wording of the Dosage and Administration section.
3. Consider revising Dosage and Administration section to recommend the same concentration of OralTag, [REDACTED] (b) (4)  
[REDACTED] If this approach is objectionable, please justify the objection.

4. The range of (b) (4) to 750 mL listed in Dosage and Administration section for Pediatrics is outside the range of the table presented in (b) (4) section. Revise one or both items to attain consistency. Consider adding a table to Dosage and Administration section that specifies pediatric doses across ages and body sizes.
5. You state that (b) (4)  
(b) (4) What is the source of this information?

We have the following recommendation in relation to the **Container, Foil and Carton Labels:**

**Container Label**

6. Revise the container label to support the measurement of volume found in the Dosage and Administration section of the package insert for pediatric patients.
7. Delete the (b) (4) from the (b) (4) box.
8. Rearrange the following phrases on the container label:

Single-use bottle  
Contains 9.7 g of iohexol powder  
(equivalent to 4.5 g of (b) (4) bound iodine)

Change to the following;

9.7g of Iohexol Powder  
(equivalent to 4.5 g of (b) (4) bound Iodine)  
Single Use Bottle-Discard Unused Portion

9. Relocate the NDC number to the upper one-third of the container label.
10. Delete the following statements from the container label: (b) (4)  
(b) (4)

**Foil Label**

11. Delete the (b) (4) from the (b) (4) box.

**Carton Label**

12. Delete the statement [REDACTED] (b) (4)

**Pharmacology Information Request**

13. We refer to the proposed Oraltag™ PI statement, [REDACTED] (b) (4)  
[REDACTED] (Oraltag™ PI, Section 8.1). Please state the route of administration used in the rat and rabbit studies on which the statement is based.

14. The Omnipaque™ PI states “Reproduction studies in rats and rabbits with doses up to 100 times the recommended human dose...” (Omnipaque™ PI, 2010; Section II, Precautions). In your Section 8.1 statement, specify the clinical dose and route of administration on which the comparisons are based. For example, if the referenced studies used the intravascular route, [REDACTED] (b) (4)  
[REDACTED] should be used.

You should respond to this request by January 6, 2014.

If you have any questions, call James Moore, Regulatory Health Project Manager, at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Acting Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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JAMES W MOORE  
12/24/2013

ALEXANDER GOROVETS  
12/24/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: December 11,2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s. Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9899
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> FDA Response to Otsuka IR, November 7, 2013, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover: 6**

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December 11, 2013

Regarding your document dated November 6, 2013 for your pending NDA 205-383 for OralTag (Iohexol) for Oral Solution, the Division has the following responses. FDA's responses appear in red font in this document. Only information from your November 6, 2013 document pertaining to Otsuka's questions 1, 2 and 3 are included in this document.

Otsuka Background to Question 1:

The FDA information request of 28-Oct-2013 and questions are presented in bold type and the answers discussed during the FDA-Company teleconference of 4-Nov-2013 follow immediately below each question.

*As agreed during the T-con, the applicant is providing questions for the NDA review team and the applicant's proposals. The company new questions and proposals are provided in this submission of 8-Nov-2013 and indicated by italics.*

**Question 1:**

**1. Given that a (b) (4), which manufacturing facility was used to generate the production and stability batch data included in the NDA?**

As described in NDA 205383 and in the attached, recent e-mail to the Division, the manufacturing facility used to generate the production and stability batch data for Iohexol (b) (4) Oral Solution included in the NDA was Ultra Seal, in New Paltz, New York. Iohexol (b) (4) Oral Solution is a drug product developed specifically for oral use and is nonsterile. The drug product is (b) (4)

An (b) (4) Ultra Seal, (b) (4) was intended to be used for commercial production of Iohexol (b) (4) Oral Solution and was described in the NDA. (b) (4) was used to make the stability batches described in the NDA, both the formal stability batches (USC04106010, USC05602010 and USC05702010) and the supportive stability batch (USC6010). (b) (4)

(b) (4) used to manufacture the Iohexol (u) (4) Oral Solution drug product at Ultra Seal as described in the NDA.

(Please note that because (b) (4) )

Subsequent to submitting the NDA to the FDA, Ultra Seal determined that (b) (4) (b) (4), was needed (b) (4).

The decision was made to (b) (4) commercial production of Iohexol (u) (4) Oral Solution.

The (b) (4) will duplicate the operating principles of the (b) (4) described in the NDA. The components of the (b) (4) will operate under the same design principles as the (b) (4)

described in the NDA and used to manufacture the stability batches. See the table below for a comparison of the [REDACTED] (b) (4)

[REDACTED] (b) (4)

*The applicant commits to completing the following items prior to the pre-approval inspection (PAI) at Ultra Seal [REDACTED] (b) (4)*

- *Installation of equipment and performance of equipment qualification (IQ, OQ)*
- *Preparation of the process validation protocol*
- *Release testing on two qualification batches of drug product manufactured [REDACTED] (b) (4) and tested by Interpharma Praha (the listed manufacturer for product release testing) against the proposed product specification.*

*As requested by the FDA in the teleconference (4 November 2013), Ultra Seal and the applicant will maintain open communications with the New York District Office about the completion of these items and timing of the PAI.*

Otsuka's Question 1:

***We believe that these steps will be sufficient to support completion of the PAI and complete the NDA review. Does the FDA concur?***

**FDA's Response to Otsuka's Question 1:**

Yes, the release data on two qualification batches of drug product (b) (4) are acceptable for review before the application's action date (approval). The release data should include the revised NDA specifications which include Free Iodine and Free Iodide tests.

Ultra Seal should demonstrate readiness to manufacture, conformance to the application, and robust data integrity as described in Compliance Program Guidance Manual 7346.832, *Pre-Approval Inspections*. This evaluation is performed during on-site inspection. Please refer to 21 CFR parts 211 and 212; Compliance Program Guidance Manual 7346.832, *Pre-Approval Inspections*; and applicable guidances in preparing for inspection. Upon readiness for inspection, Ultra Seal should contact the FDA New York District Office.

**Otsuka's Background to Question 2:**

***Under what conditions was the production and stability batch ( (b) (4) equipment, etc.) data in the NDA obtained?***

The formal stability batches described in the NDA were manufactured under CGMPs at Ultra Seal on (b) (4) according to an approved development protocol (Ultra Seal (b) (4)), with batch records produced, and compliant with Ultra Seal Standard Operating Procedures. See the table above for a list of equipment configured (b) (4) the manufacturing runs.

During early development runs, it was determined (b) (4)

(b) (4)

One component of the equipment described in the NDA for the final commercial process, (b) (4)

(b) (4)

***Applicant Question #2:***

*We consider that stability data previously generated using (b) (4) fully representative of the to-be-marketed product. According to ICH guidance Q1A (R2) there is no requirement for primary stability batches to be manufactured (b) (4) as long as the process used is fully representative of the proposed commercial process (see also Figure 3.2.P.3.3.1 in the NDA).*

However, as data accrue on the qualification batches (see response to Applicant Question #1 above) they will provide a link between the stability data provided from [REDACTED] (b) (4).

Iohexol drug substance and the Iohexol [REDACTED] (b) (4) Oral Solution drug product are very stable as demonstrated by primary stability data included in the NDA (24months on the drug substance and 18 months on the drug product.)

Otsuka's Question 2:

*Does the FDA agree that the existing and proposed stability programs (see also the proposal in Applicant Question #3 below) are sufficient to characterize the product?*

**FDA's Response to Otsuka's Question 2:**

Yes, as long as there is comparability between the past stability studies on batches produced [REDACTED] (b) (4)

Otsuka's Background to Question 3:

**What is your timeline for bringing the New York Facility on line for manufacture of the commercial product?**

Below is a summary of the timeline [REDACTED] (b) (4)  
[REDACTED] (b) (4)

[REDACTED] (b) (4)

***Applicant Question #3***

*The applicant proposes to complete the following items as potential postmarketing commitments:*

- *Initiate stability program, including [REDACTED] (b) (4) test points for longterm and accelerated stability data on 2 qualification batches of drug product manufactured [REDACTED] (b) (4)*

(b) (4) Note that stability data will continue to accrue on the qualification batches and these will be reported in upcoming Annual Reports.)

- Initiate and complete (b) (4)
- Initiate postapproval stability program on first 3 commercial lots

Otsuka's Question 3:

Does the FDA concur with this proposal to complete and report (b) (4) and future stability activities?

**FDA's Response to Otsuka's Question 3:**

No. The recommendation is to test two of the qualification batches for six months under long term and accelerated conditions. The data may be provided to the NDA as a post-approval commitment or at the time of resubmission as applicable.

To initiate the post-approval stability program on the first 3 commercial lots is acceptable.

**If you have additional questions, contact me at (301) 796-1986.**

**James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES W MOORE  
12/11/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: December 11, 2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s. Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9899
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> Minutes of Telephone Conference November 4, 2013, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover: 9**

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# MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** November 4, 2013

**Application Number:** N205-383

**Product Name:** OralTag (Iohexol) (b) (4) Oral Solution

**Sponsor/Applicant Name:** Interpharma Praha, a.s., U.S Agent, Otsuka

**Subject:** Discussion of Chemistry IR Questions Dated October 28, 2013

**FDA Participants :** Milagros Salazar-Driver, Ph.D., Chemistry Reviewer, ONDQA  
Eldon Leutzinger, Ph.D., Chemistry Lead, ONDQA  
Diana Christodoulou, Ph.D, Branch Chief, ONDQA  
Tien Mien Chen, Ph.D., OPS/ONDQA  
Barbara Stinson, D.O., Clinical Reviewer, DMIP  
Robert Wittorf, PharmD, OC  
Jessica Cole, Ph.D., Microbiologist, OPS  
Mahesh Ramanadham, PharmD, OC  
Matthew Spataro, OC  
Frank Verni, OC  
James Moore, PharmD., M.A., Regulatory Health Project Manager, DMIP

**Sponsor/Applicant Participants :** Scott Hollander, Vice President Otsuka, Medical Imaging, CEO, Interpharma Praha  
Joel Timberlake, Vice President Manufacturing, Otsuka Medical Imaging  
Marjory Kadash, M.S., Director, Regulatory Affairs, Otsuka  
Yoshito Masuda, M.S., RPh., Director Easter European Office, Interpharma Praha, a.s.  
Usha Kidambi, M.S.P.M.P, Associate Director Program Management Otsuka

## 1.0 BACKGROUND:

This telephone conference was requested by FDA to discuss the Ultra Seal Manufacturing Facility in New Paltz, NY. This was based on a report from the FDA field Office that stated the facility was not ready for a Prior Approval Inspection (PAI).

FDA prepared an information request that was sent to Otsuka prior to the telephone conference. Otsuka prepared a response to FDA's IR and that response was the subject of the telephone conference. The discussion focused on Otsuka's plan for the manufacturing facility and submissions needed from Otsuka before completion of the review process. A copy of the Otsuka response can be found in section 4 of this document.

## 2.0 DISCUSSION:

FDA discussed the following topics with Otsuka:

- (1) The timing for bringing the New Paltz, NY facility on line so that it was ready for a Pre-Approval Inspection.
- (2) The need for the production of several representative commercial batches of the to be marketed product manufactured at the New Paltz, New York facility prior to issue of an action letter for the application.

- (3) Identification of the building at the New Paltz, NY site that will be used to manufacture the marketed product.
- (4) The need for Otsuka to provide stability data on the commercial batches prior to the final action by FDA on the application.
- (5) Validation of equipment for (b) (4) production of the Iohexol product.
- (6) The need for bridging data from (b) (4)
- (7) Quality data obtained on production batches after (b) (4)
- (8) The timing for completion of the protocol required for the manufacture of the Iohexol product, facility maintenance, and quality control in the manufacturing facility including actions that must be completed prior to the Prior Approval Inspection.
- (9) Fill Weights and the Container Closure System.
- (10) The number and types of stability batches that are required for review under the pending NDA.

Otsuka stated the following during the discussion:

- (1) Commercial line 3 will be used to manufacture the commercial product.
- (2) Batches of the product have been manufactured (b) (4) of the New Paltz manufacturing facility that are similar to those that will be manufactured (b) (4)
- (3) Otsuka can't provide a definitive date when the New Paltz, New York facility will be ready for inspection, but estimated that the standard manufacturing protocol would be ready in mid-January.
- (4) Batches already produced and those generated (b) (4) in the New York facility should be sufficient for the stability required in the NDA.
- (5) Stability batches as a Post Marketing Requirement after approval of the product could be provided.

**Summary**

FDA did not commit/agree to any Post Marketing proposals suggested by Otsuka. FDA did communicate to Otsuka that the Agency was open to assisting and providing guidance to Otsuka towards readying the New Paltz facility for inspection. FDA recommended to Otsuka that they work closely with the FDA's District office and Ultra Seal to accomplish this goal.

Otsuka described their proposed manufacture of Iohexol and how the container-closure system would be incorporated in the process.

**3.0 ACTION ITEMS:**

1. Ultraseal must complete their Standard Operating Procedures before a Prior Approval Inspection is scheduled.
2. Commercial (b) (4) Ultra Seal at the New Paltz, NY site must be ready for inspection before there is a discussion on the approvability of the product.
3. Otsuka should work closely with Ultra Seal and the District office to facilitate the manufacturing site's readiness for inspection.
4. Otsuka must provide release data, a minimum of 12 months long term stability (CRT) data, and 6 months data under accelerated conditions for 2 batches (b) (4) at Ultra Seal.

**4.0 Otsuka Response of November 1, 2013**

**Quality Information Amendment**

The following information is provided in response to the FDA information request of October 28, 2013. The questions are presented in **bold type** and the answers follow immediately below each question.

- 1. Given that a (b) (4) is not currently operational, which manufacturing facility was used to generate the production and stability batch data included in the NDA?**

As described in NDA 205383 and in the attached, recent e-mail to the Division, the manufacturing facility used to generate the production and stability batch data for Iohexol (b) (4) Oral Solution included in the NDA was Ultra Seal, in New Paltz, New York. Iohexol (b) (4) Oral Solution is a drug product developed specifically for oral use and is nonsterile. The drug product (b) (4)

(b) (4) was intended to be used for commercial production of Iohexol (b) (4) Oral Solution and was described in the NDA. (b) (4) was used to make the stability batches described in the NDA, both the formal stability batches (USC04106010, USC05602010 and USC05702010) and the supportive stability batch (USC6010).

(b) (4) used to manufacture the Iohexol (b) (4) Oral Solution drug product at Ultra Seal as described in the NDA. (Please note that because (b) (4)

Subsequent to submitting the NDA to the FDA, Ultra Seal determined (b) (4). The decision was made (b) (4) (b) (4) (b) (4)

The components of the new integrated (b) (4) will operate under the same design principles as the components (b) (4) described in the NDA and used to manufacture the stability batches. See the table below for a comparison of (b) (4).

**Table 1 Comparison of Equipment** (b) (4) **Ultra Seal**

(b) (4)



**2. Under what conditions was the production and stability batch ( (b) (4) equipment, etc.) data in the NDA obtained?**

The formal stability batches described in the NDA were manufactured under CGMPs at Ultra Seal on (b) (4), according to an approved development protocol (Ultra Seal (b) (4)), with batch records produced, and compliant with Ultra Seal Standard Operating Procedures. See the table above for a list of equipment configured (b) (4) for the manufacturing runs.

During early development runs, it was determined that (b) (4)  
(b) (4)  
(b) (4)  
(b) (4)  
(b) (4).

One component of the equipment described in the NDA for the final commercial process, the (b) (4)  
(b) (4)  
(b) (4)

**3. Why was the New York facility not ready for inspection?**

As communicated in the recent e-mail to the Division, to the best of our knowledge, when the NDA was submitted, the New York facility was ready for inspection.

When the need for Ultra Seal (b) (4) was confirmed, after the NDA was submitted, we reviewed applicable FDA regulations and guidance. We consulted with outside regulatory advisors. A mock pre-approval inspection (PAI) was performed at Ultra Seal by a former FDA investigator; the conclusion of the investigator was that Ultra Seal was prepared for a PAI to support the Iohexol (b) (4) product.

Based on our understanding, the PAI could be performed because (b) (4) used to make the stability batches and related documentation was available for inspection. As indicated above (b) (4)

(b) (4)  
(b) (4)  
(b) (4)

**4. Why isn't the commercial manufacturing line in place when there was a written statement in the NDA that it was and this was one of the conditions for filing?**

As explained above, at the time that the NDA was prepared and submitted, the commercial manufacturing (b) (4) was in place at Ultra Seal in New York and ready for inspection. (b) (4)

(b) (4)  
(b) (4). After the NDA submission, a decision was made to (b) (4) for Iohexol (b) (4) Oral Solution: (b) (4) by Ultra Seal. The (b) (4) is designed to duplicate the operating principles of the (b) (4) described in the NDA and the development data included therein. Therefore we did not amend the NDA with respect to inspection-readiness.

(b) (4)  
(b) (4)

(b) (4) Iohexol Powder will be fully qualified and validated prior to commercial distribution.

**5. What is your timeline for bringing the New York Facility on line for manufacture of the commercial product?**

Below is a summary of the timeline for (b) (4)

(b) (4)

**6. How soon will the Standard Operating Procedures for the New York manufacturing facility be complete and operational?**

A comprehensive set of Standard Operating Procedures (SOPs) are in place at the Ultra Seal New York facility and the manufacturing facility is fully operational. The procedures are consistent with CGMP compliance. A draft Production Master Batch Record has been prepared, according to Ultra Seal SOPs, for manufacturing the commercial lots of Iohexol (b) (4) Oral Solution (b) (4) SOPs specific to (b) (4) will be completed prior to qualification.

(b) (4). Ultra Seal's Quality System is supported by a Quality Manual and a comprehensive set of SOPs. Ultra Seal's manufacturing facility and its procedures have been regularly reviewed during numerous customer audits and during FDA inspections since 2000. In addition, the applicant conducted an audit of Ultra Seal and its Quality System as part of the vendor qualification performed to select Ultra Seal as the manufacturer of the drug product Iohexol (b) (4) Oral Solution.

**7. What are your plans to address the lack of a facility for the manufacturer of your drug product?**

Please see responses to above questions. We believe that the facility, Ultra Seal in New Paltz, New York, used to manufacture the stability batches described in the NDA is a suitable facility for manufacturing the drug product. As noted in the response to Question #5, this facility is expected to complete specific equipment qualifications of (b) (4) by the beginning of January 2014 and will be ready to begin (b) (4) following NDA approval when approved labeling is available.

**8. When will the New York facility that will manufacture the commercial product be ready for inspection?**

(b) (4) that is not the current intent for commercial production. (b) (4), the FDA Investigator from the New York District assigned to conduct the PAI, Paul Mouris, advised Ultra Seal that the (b) (4), should be installed and qualified prior to completing the PAI. The equipment for (b) (4) is expected to be installed and qualified by the beginning of January 2014. Ultra Seal has committed to inform the New York District office, and the applicant, when this is achieved.

Attachment 1

Copy of E-mail Sent to Division of Medical Imaging Products

**From:** Kadash, Marjory  
**Sent:** Friday, October 18, 2013 4:22 PM  
**To:** Moore, James W  
**Cc:** Kadash, Marjory  
**Subject:** NDA 205383: Iohexol (b) (4) Oral Solution

Dear James,

This e-mail is with reference to NDA 205383 for the drug product Iohexo (b) (4) Oral Solution.

The purpose of this e-mail is to update you on the PAI inspection at the contract manufacturer for our drug product. The contract manufacturer is Ultra Seal Corporation in New Paltz, New York. Ultra Seal is listed as a manufacturing Establishment in our 356h form for our NDA and is also included in Module 3.2.P.3.1 of our NDA.

Ultra Seal has informed us that an FDA Investigator, Paul Mouris from the New York District, arrived at the Ultra Seal facility on October 1 to perform a PAI for the Iohexol Powder product. During the opening discussions, the Investigator informed Ultra Seal that he could not complete the PAI until the (b) (4) for the drug product was installed and qualified. Consequently, the Investigator completed a full GMP inspection at Ultra Seal. The Investigator requested that Ultra Seal contact him to complete the PAI once the final equipment qualification is completed. Ultra Seal provided, at the Investigator's request, a list of the equipment and the estimated date for completion of installation and qualification, expected to be no later than the beginning of January.

We want to clarify for the review division, that when our NDA was submitted, and the 356h form was completed, we correctly stated that the Ultra Seal site was ready for inspection. All development work and formal stability samples were made on (b) (4) intended for commercial production as described in the NDA, Module 3.2.P.2.3. The module also states that process validation would be completed prior to commercialization. As described in Module 3.2.P.3.3.2, the commercial (b) (4)

Subsequent to the NDA submission, Ultra Seal determined that an (b) (4) (b) (4) would be required to meet all of Ultra Seal's (b) (4). We, the Sponsor, reached agreement with Ultra Seal that the (b) (4) would be (b) (4) Iohexo (b) (4) production. The (b) (4) where all components would duplicate the operating principles of the commercial (b) (4) described in the NDA for Iohexol Powder. Differences would be only for incorporating process and environmental improvements. We had planned to complete installation and qualification of (b) (4) to process validation and therefore prior to commercialization of the Iohexol Powder product.

Following review of FDA regulations and guidance, as well as from consultation with outside regulatory advisors, we concluded that the plan described above should not prevent completion of any FDA inspections required prior to NDA approval, such as the PAI. Consequently, we were surprised to learn that the FDA Investigator could not complete the PAI at this time.

We want you to be aware of this situation and would also like to understand if we can provide any additional information to clarify the situation. We would like to understand how the completed and anticipated inspection activity will dovetail with the existing PDUFA approval goal date of 14 Jan 2014.

This is a lengthy e-mail. I am available at your convenience to further explain the situation and our team members are also available to discuss the matter with the FDA review team.

Please let me know the next best step to ensure that the NDA review and approval process can continue as planned.

Kind regards,

Marjory

If you have questions, contact James Moore, Regulatory Health Project Manager at (301) 796-1986.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP

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/s/  
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JAMES W MOORE  
12/11/2013

MEMO 4-Nov-2013

From: Milagros Salazar, Ph.D., ONDQA, Div. III-Branch VII

Through: Eldon Leutzinger, Ph.D., ONDQA, Div. III-Branch VII

To: NDA 205-383 file

Drug: Oratag® (iohexol) (b) (4) Oral Solution

Applicant: Interpharma Praha, a.s. / Otsuka (USA representative)

Subject: Review of submission dated 6-Nov-2013/Stamp Date: 8-Nov-2013 to respond to the Applicant questions.

The FDA information request of **28-Oct-2013** and **questions are presented in bold type** and the answers discussed during the FDA-Company teleconference of 4-Nov-2013 follow immediately below each question.

*As agreed during the T-con, the applicant is providing questions for the NDA review team and the applicant's proposals. The company new questions and proposals are provided in this submission of 8-Nov-2013 and indicated by italics.*

**CMC Responses are presented after each Applicant's Question in red color font.**

**Question 1:**

**1. Given that a (b) (4), which manufacturing facility was used to generate the production and stability batch data included in the NDA?**

As described in NDA 205383 and in the attached, recent e-mail to the Division, the manufacturing facility used to generate the production and stability batch data for Iohexol (b) (4) Oral Solution included in the NDA was Ultra Seal, in New Paltz, New York. Iohexol (b) (4) Oral Solution is a drug product developed specifically for oral use and is nonsterile. The drug product (b) (4)

(b) (4), was intended to be used for commercial production of Iohexol (b) (4) Oral Solution and was described in the NDA. (b) (4) used to make the stability batches described in the NDA, both the formal stability batches (USC04106010, USC05602010 and USC05702010) and the supportive stability batch (USC6010). (b) (4) currently operational and could be used to manufacture the Iohexol (b) (4) Oral Solution drug product at Ultra Seal as described in the NDA.

(b) (4)  
(b) (4)

Subsequent to submitting the NDA to the FDA, Ultra Seal determined (b) (4)

(b) (4)

(b) (4) will duplicate the operating principles of the (b) (4) described in the NDA. The components of the (b) (4) will operate under the same design principles as the components of (b) (4) described in the NDA and used to manufacture the stability batches. See the table below for a comparison (b) (4)

**Table 1 Comparison of Equipment**

(b) (4)

(b) (4)

***Applicant Question #1:***

*The applicant commits to completing the following items prior to the pre-approval inspection (PAI) at Ultra Seal* (b) (4)

(b) (4)

*As requested by the FDA in the teleconference (4 November 2013), Ultra Seal and the applicant will maintain open communications with the New York District Office about the completion of these items and timing of the PAI.*

*We believe that these steps will be sufficient to support completion of the PAI and complete the NDA review. Does the FDA concur?*

**CMC Response: Yes, the release data on two qualification batches of drug product from (b) (4) are acceptable for review before the application's action date (approval). The release data should include the revised NDA specifications which include Free Iodine and Free Iodide tests.**

**2. Under what conditions was the production and stability batch ( (b) (4) equipment, etc.) data in the NDA obtained?**

The formal stability batches described in the NDA were manufactured under CGMPs at Ultra Seal on the (b) (4) according to an approved development protocol (Ultra Seal

(b) (4), with batch records produced, and compliant with Ultra Seal Standard Operating Procedures. See the table above for a list of equipment configured on the (b) (4) for the manufacturing runs.

During early development runs, (b) (4)

One component of the equipment described in the NDA for the final commercial process, (b) (4)

### ***Applicant Question #2:***

*We consider that stability data previously generated using (b) (4) is fully representative of the to-be-marketed product. According to ICH guidance Q1A (R2) there is no requirement for primary stability batches to be manufactured on the commercial line as long as the process used is fully representative of the proposed commercial process (see also Figure 3.2.P.3.3.1 in the NDA).*

*However, as data accrue on the qualification batches (see response to Applicant Question #1 above) they will provide a link between the stability data provided from (b) (4) previously submitted to the NDA and (b) (4)*

*Iohexol drug substance and the Iohexol (b) (4) Oral Solution drug product are very stable as demonstrated by primary stability data included in the NDA (24months on the drug substance and 18 months on the drug product.)*

***Does the FDA agree that the existing and proposed stability programs (see also the proposal in Applicant Question #3 below) are sufficient to characterize the product?***

**CMC Response: Yes, as long as there is comparability between the past stability studies on batches produced in (b) (4)**

### **3. Why was the New York facility not ready for inspection?**

As communicated in the recent e-mail to the Division, to the best of our knowledge, when the NDA was submitted, the New York facility was ready for inspection. When the need for Ultra Seal to construct an (b) (4), after the NDA was submitted, we reviewed applicable FDA regulations and guidance. We consulted with outside regulatory advisors. A mock PAI was performed at Ultra Seal by a former FDA investigator; the conclusion of the investigator was that Ultra Seal was prepared for a PAI to support the Iohexol Powder product.

Based on our understanding, the PAI could be performed because (b) (4) used to make the stability batches and related documentation were available for inspection. As indicated above, because (b) (4) at the time the FDA inspector arrived to conduct the PAI. (b) (4)

**4. Why isn't the commercial (b) (4) in place when there was a written statement in the NDA that it was and this was one of the conditions for filing?**

As explained above, at the time that the NDA was prepared and submitted, the commercial (b) (4) was in place at Ultra Seal in New York and ready for inspection. (b) (4)

After the NDA submission, a decision was made to construct (b) (4) for Iohexol Oral Solution; this would address the (b) (4) identified by Ultra Seal. The (b) (4) is designed to duplicate the operating principles of the (b) (4) described in the NDA and the development data included therein. Therefore we did not amend the NDA with respect to inspection-readiness.

(b) (4)  
(b) (4) to Iohexol Powder will be fully qualified and validated prior to commercial distribution.

**5. What is your timeline for bringing the New York Facility on line for manufacture of the commercial product?**

Below is a summary of the timeline for the (b) (4) (b) (4)

***Applicant Question #3***

*The applicant proposes to complete the following items as potential postmarketing commitments:*

- *Initiate stability program, including (b) (4) test points for longterm and accelerated stability data on 2 qualification batches of drug product manufactured on (b) (4) (Note that stability data will continue to accrue on the qualification batches and these will be reported in upcoming Annual Reports.)*
- *Initiate and complete (b) (4)*
- *Initiate postapproval stability program on first 3 commercial lots*

***Does the FDA concur with this proposal to complete and (b) (4) and future stability activities?***

**CMC Response: No. The recommendation is to test two of the qualification batches for six months under long term and accelerated conditions. The data may be provided to the NDA as a postapproval commitment or at the time of resubmission as applicable.**

**To initiate the postapproval stability program on the first 3 commercial lots is acceptable.**

File name: NDA 205-383 FDA responses to 8-Nov-2013 Applicant questions.doc

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/s/  
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MILAGROS SALAZAR DRIVER

12/04/2013

CMC responses to share with applicant.

ELDON E LEUTZINGER

12/04/2013

**PeRC PREA Subcommittee Meeting Minutes  
November 13, 2013**

**PeRC Members Attending:**

Lynne Yao  
Hari Cheryl Sachs  
Karen Davis-Bruno  
Julia Pinto ( (b) (4) reviews only)  
William J. Rodriguez  
Peter Starke  
Wiley Chambers  
Lily Mulugeta  
Daiva Shetty  
Andrew Mulberg  
Coleen LoCicero  
Barbara Buch ( (b) (4) reviews only)  
Dianne Murphy  
Adrienne Hornatko-Munoz ( (b) (4) reviews only)  
Gregory Reaman  
Dionna Green  
Robert "Skip" Nelson  
Lisa Kammerman  
Jane Inglese  
Rachel Witten  
Susan McCune  
George Greeley

**Guests Attending:**

Nichella West (PMHS)	Theresa Finn (CBER)
Erica Radden (PMHS)	Karen Farizo (CBER)
Donna Snyder (PMHS)	Megann Ferris (CBER)
Paula Agger (CBER)	Mike Smith (CBER)
Sammie Beam (DAVP)	Kirk Chan-Tacu (DAVP)
Mary Singer (DAVP)	Nikolay Nikolov (DPARP)
Juwaria Waheed (DPARP)	Satjjiot Brar (OCP)
Yuliya Yasinskaya (DAIP)	Carmen DeBellas (DAIP)
Satjit Brar (OCP)	Terry Harrison (DPP)
Brenda Baldwin (CBER)	Andrea James (CBER)

**Agenda**

9:30 (b) (4)  
9:50  
10:10

(b) (4)

(b) (4)

NDA 205383 Iohexol Appropriately Labeled

(b) (4)

(b) (4)

(b) (4)

(b) (4)

**Iohexol Assessment**

- NDA 205383 seeks marketing approval for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. (b) (4)  
[Redacted]
- The application has a PDUFA goal date of January 10, 2014.
- The application triggers PREA as a new dosage form.
- *PeRC Recommendations:*
  - The PeRC agreed that an assessment has been presented in pediatric patients (b) (4)  
[Redacted] because it was previously appropriately labeled.

(b) (4)

(b) (4)



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/s/  
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GEORGE E GREELEY  
11/25/2013

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your *current submission*.**

***Definitions:***

***Deferral*** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

***Full Waiver*** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

***Partial Waiver*** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

***Pediatric Assessment*** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness

*of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.*

***Pediatric Plan*** – *A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.*

***Pediatric Population/Patient***- *21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.*

***PREA Pediatric Record/Pediatric Page*** – *The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.*

# Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

## BACKGROUND

Please check all that apply: Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

BLA/NDA#: 205-383

PRODUCT PROPRIETARY NAME: OralTag <sup>(b) (4)</sup> Oral Solution ESTABLISHED/GENERIC NAME: Iohexol  
APPLICANT/SPONSOR: Interpharma Praha, a.s., U.S Agent: Otsuka Pharmaceuticals

PREVIOUSLY APPROVED INDICATION/S: None

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

PROPOSED INDICATION/S:

(1) *For oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis.* <sup>(b) (4)</sup>

BLA/NDA STAMP DATE: March 11, 2013

PDUFA GOAL DATE: January 10, 2014

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

**Does this application provide for (If yes, please check all categories that apply and proceed to the next question):**

**NEW**  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?

**Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)**

Yes  No

**Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes  No**

**If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_**

**Does the division agree that this is a complete response to the PMR? Yes  No**

**If Yes, to either question Please complete the Pediatric Assessment Template.**

**If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.**

**PeRC ASSESSMENT TEMPLATE**

*Please attach:*

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

**Date of PREA PMR:**

**Description of PREA PMR:** *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC?  **Yes**  **No** If yes, did sponsor follow plan?

**If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.**

**Indication(s) that were studied:**

This section should list the indication(s) exactly as written in the *protocols*.

*Example:*

*DRUG for the treatment of the signs and symptoms of disease x.*

**Number of Centers** \_\_\_\_\_

**Number and Names of Countries** \_\_\_\_\_

**Drug information:**

*Examples in italics*

- **Route of administration:** *Oral*
- **\*Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

*\*If the dosage form is (b) (4) oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

**Types of Studies/ Study Design:**

*Example:*

*Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.*

*Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*

**Age group and population in which study/ies was/were performed:**

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients studied or power of study achieved:**

*Example:*

*Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.*

*Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .*

**Entry criteria:**

This section should list pertinent inclusion/exclusion criteria.

*Example:*

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs*

*Patients had a negative pregnancy test if female.*

**Clinical endpoints:**

*Example:*

*Study 1: Clinical outcome and safety were the primary endpoints.*

*Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*

**Statistical information (statistical analyses of the data performed):**

This section should list the statistical tests conducted.

*Example:*

*Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.*

*Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*

**Timing of assessments:**

*Example:*

*Baseline, week 2, week, 6, and end of treatment*

**Division comments on product efficacy:**

**This application relies on the Reference Listed Drug (RLD) for support of its safety and efficacy. No clinical trials were submitted in the application.**

**Division comments on sponsor proposal to satisfy PREA: Consistent with the 505(b)(2) application, based on the prior FDA approval(s) for use of OMNIPAQUE in all pediatric age groups and supported by the review of the literature, a waiver to conduct clinical trial studies in all pediatric age groups is requested. Efficacy and safety has already been demonstrated in all pediatric age groups. Clinical experience studies have been completed and published for all PREA defined age groups, including neonates.**

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/s/  
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JAMES W MOORE  
11/12/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: October 28,2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> Chemistry Questions for Telephone Conference, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover: 2**

**Comments:** These comments are draft and are subject to addition, deletion, or revision. FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). The comments were sent via email to the Sponsor.

**Document to be mailed:** YES  NO

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October 28, 2013

Regarding your pending NDA 205-383, for Iohexol (b) (4) Oral Solution, the review team wishes to discuss the following questions in a telephone conference with your company.

1. Given that (b) (4), which manufacturing facility was used to generate the production and stability batch data included in the NDA?
2. Under what conditions was the production and stability batch ( (b) (4) equipment, etc.) data in the NDA obtained?
3. Why was the New York facility not ready for inspection?
4. Why isn't the commercial (b) (4) in place when there was a written statement in the NDA that it was and this was one of the conditions for filing?
5. What is your timeline for bringing the New York Facility on line for manufacture of the commercial product?
6. How soon will the Standard Operating Procedures for the New York manufacturing facility be complete and operational?
7. What are your plans to address the lack of a facility for the manufacturer of your drug product?
8. When will the New York facility that will manufacture the commercial product be ready for inspection?

Please provide as soon as possible your contact information for the telephone conference and your availability to discuss these questions.

If you have questions, contact James Moore, Regulatory Health Project Manager at (301) 796-1986.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP

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/s/  
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JAMES W MOORE  
10/29/2013



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation OODP**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: September 13, 2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> Chemistry Information Request, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover: 2**

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**Document to be mailed:** YES                      x NO

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September 13, 2013

Regarding your pending NDA 205-383 for OralTag (Iohexol) for Oral Solution, the reviewing chemist has the following information requests and comments.

1. Provide data for free iodine content in the primary stability lots of iohexol (b) (4) oral solution.
2. Submit data for free iodide ( $\mu\text{g}$  per g of iohexol and  $\mu\text{g}$  per mL of oral solution) in the primary stability lots of iohexol (b) (4) the final oral solution product. Provide the results with the exact value found, rather than a general statement of (b) (4)
3. Provide a revised list of specifications (test and limits) for free iodine and free iodide in the iohexol (b) (4) oral solution product. The specifications must be part of the release criteria and the stability studies for your product as it is for all other iodinated contrast media on the market.
4. Provide a commitment to test and monitor the content of free iodide in the final product at the next obtainable stability time point and up to the end of the proposed stability studies. The test results may be reported as a Phase IV study, in an annual report or as an amendment to the NDA if approved.
5. Provide photostability study, following ICH Q1B, monitoring free iodide and free iodine content. A control sample of Omnipaque should be included. The test results may be reported as a Phase IV study, in an annual report or as an amendment to the NDA depending of the NDA approval status.

Provide this information to me electronically by October 2, 2013 at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov). Follow up with a submission to your pending NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP

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/s/  
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JAMES W MOORE  
09/13/2013



NDA 205383

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Interpharma Praha, a.s.  
c/o: Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development and Commercialization, Inc.  
1 University Square Drive  
Suite 500  
Princeton, NJ 08540

ATTENTION: Marjory Kadash  
Director, Regulatory Affairs

Dear Ms. Kadash:

Please refer to your New Drug Application (NDA) dated and received March 11, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Iohexol (b) (4) Oral Solution, 9.7grams.

We also refer to your May 31, 2013, correspondence received June 5 2013, requesting review of your proposed proprietary name, Oraltag.

We have completed our evaluation of the proposed proprietary name and have concluded that this name is acceptable for this oral formulation.

The proposed proprietary name, Oraltag, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 31, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, James Moore at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
08/30/2013



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: May 31, 2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> Safety Update Response, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover:** 2

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May 31, 2013

Regarding your inquiry about the requirement to submit a Safety Update (b) (4)  
 for your pending NDA 205-383 (Iohexol), the Division has the following response.

Periodic safety updates are required under 21 CFR 314.50(d)(3)(b), including the “120 day safety update.” However, the content of the safety update report(s) is determined by what you learn about clinical safety concerns, nonclinical data that show safety concerns or other sources of important safety information that “may reasonably affect” the labeling for your drug. Because your clinical experience appears to derive from published literature and any post-marketing experience (outside the USA), we anticipate that you currently monitor the published literature and monitor your own receipt of any safety concerns regarding your drug. During your ongoing monitoring of safety during the application review time period, if you detect no new safety concerns that may reasonably affect your drug labeling, then your NDA safety update(s) should make this statement and briefly summarize the basis for the statement.

(b) (4)

If you have additional questions, please don't hesitate to contact me at (301) 796-1986.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP

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/s/  
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JAMES W MOORE  
06/03/2013

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Medical Imaging Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call James Moore, Regulatory Health Project Manager, at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Rafel D. Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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JAMES W MOORE  
05/09/2013

RAFEL D RIEVES  
05/09/2013



NDA 205-383

**NDA ACKNOWLEDGMENT**

Interpharma Praha, a.s.  
C/O Otsuka Novel Products, Medical Imaging  
Attention: Marjory Kadesh  
US Agent for Interpharma Praha, a.s.  
Director, Regulatory Affairs  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540

Dear Ms. Kadesh:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (iohexol) (b) (4) Oral Solution

Date of Application: March 11, 2013

Date of Receipt: March 11, 2013

Our Reference Number: NDA 205-383

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 May 10, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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 Medical Imaging Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

James Moore, PharmD., M.A.  
Regulatory Health Project Manager  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

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/s/  
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JAMES W MOORE  
04/03/2013



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: April 3, 2013**

<b>To:</b> Marjory Kadash	<b>From:</b> James Moore
<b>Company:</b> US Agent for Interpharma Praha, a.s Otsuka Novel Products, Medical Imaging	Division of Medical Imaging Products
<b>Fax number:</b> (240) 514-3876	<b>Fax number:</b> (301) 796-9849
<b>Phone number:</b> (609) 524-6875	<b>Phone number:</b> (301) 796-1986
<b>Subject:</b> Chemistry Request1, NDA 205-383, Iohexol, (b) (4) Oral Solution	

**Total no. of pages including cover:** 2

**Comments:** These comments are draft and are subject to addition, deletion, or revision. FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). The comments were sent via email to the Sponsor.

**Document to be mailed:** YES                      x 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) 796-2050. Thank you.

April 3, 2013

Regarding your pending NDA for Iohexol, NDA 205-383, the reviewing chemist has the following comments and information requests.

1. Explain why the 12 months long term stability for Iohexol (b) (4) oral solution was not included in the NDA as recommended in the Pre-NDA meeting minutes (19-Apr-12) and in Facsimile on Questions 3 and 8 for CMC (23-May-2012). This data was expected to be in the NDA submission to support the filing of this application.
2. Provide a timeline for the submission of the stability data in electronic format with statistical analysis of all stability-indicating quality parameters.
3. Provide information regarding the release of the drug product responsibilities for (b) (4) and specify what kind of testing, if any, is conducted in this establishment.
4. Submit a statement of readiness for inspection and the FEI and DUNS numbers for the Ultra Seal Corporation-New Paltz, NY and the (b) (4) establishments.
5. If (b) (4) does not perform release testing for the final drug product clarify, where this test is performed?

Provide this information to me electronically at [James.Moore@fda.hhs.gov](mailto:James.Moore@fda.hhs.gov) and follow up with a submission to your pending NDA file. You should provide your response to FDA by COB, Wednesday, April 10, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager, DMIP

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/s/  
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JAMES W MOORE  
04/03/2013



IND 114,359

**MEETING MINUTES**

Otsuka Pharmaceutical Development & Commercialization, Inc.  
Attention: Marjory Kadash  
Director, Regulatory Affairs  
Otsuka Novel Products, Medical Imaging  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540

Dear Ms. Kadash:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Iohexol.

We also refer to the meeting between representatives of your firm and the FDA on March 20, 2012 from 12 PM-1 PM. The purpose of the meeting was to discuss plans to submit an NDA for Iohexol (b) (4) Oral Solution and receive Agency feedback on the proposed drug product and use of the 505(b)(2) regulatory pathway for marketing approval of Iohexol.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call James Moore, Regulatory Health Project Manager at (301) 796-1986.

Sincerely,

*{See appended electronic signature page}*

Rafel D. Rieves, M.D.  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

Industry Meeting between Otsuka Pharmaceuticals and the Division of Medical Imaging Products, Tuesday, March 20, 2012, 12PM-1PM, White Oak Campus, Building 22, Conference Room 1415, Silver Spring, Maryland

Subject: I 114,359, Iohexol Pre-NDA Meeting, 505(b)(2) Discussion

FDA Attendees:

Rafel D. Rieves, M.D., Director, DMIP  
Liberio Marzella, M.D., Ph.D., Deputy Director, DMIP  
Alexander Gorovets, M.D., Clinical Team Leader, DMIP  
Barbara Stinson, D.O., Clinical Reviewer, DMIP  
Sally Hargus, Ph.D., Pharmacology/Toxicology Reviewer, DMIP  
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader, DMIP  
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, OCP  
Satish Misra, Ph.D., Statistical Reviewer, OB  
James Moore, PharmD., M.A., Regulatory Health Project Manager, DMIP

Otsuka Attendees:

Ivan Hlavacek, Chief Operating Officer, Interpharma Praha  
Barry Hogstrom, Vice President Medical Affairs  
Scott Hollander, Chief Executive Officer, Interpharma Praha  
Nobuhiro Ikei, Director Eastern Europe Office  
Marjorie Kadash, Director, Regulatory Affairs  
Yosuke Maki, Executive Vice President, Interpharma Praha  
Anne Paccaly, Director Clinical Pharmacology  
Joel Timberlake, Vice President, Manufacturing  
Masuhiro Yoshitake, Executive Operating Officer

(b) (4)

**Background**

Prior to the meeting a letter was sent to Otsuka Pharmaceuticals that contained the Division's preliminary comments in response to the questions contained in Otsuka's meeting package dated February 13, 2012. After introductions the meeting began.

## **Product and Regulatory Questions**

### *Sponsor's Question 1:*

The applicant is proposing that Iohexol Powder will be indicated for oral use as an opacification agent during CT of the abdomen.

*Does the FDA agree with the proposed route of administration and indication?*

### **FDA's Response 1:**

**Information you have provided in the meeting package is insufficient to enable us to fully address your question at this time. Please provide more detailed information on the proposed indication for your product and its intended use, for example the target population, whether there will be a general indication for oral use or whether the indication will be limited to CT, whether the product will be used to study disorders of the GI tract or whether the use will be solely as an adjunct to improve abdominal-pelvic CT diagnosis. Please comment on any intentions to use your product in the same manner as the currently approved Omnipaque, i.e. whether you also plan to develop this as a solution for iv use. Please provide a list of countries in which your product is currently approved and, if approved, a sample of approved indications.**

### *Sponsor's Question 2:*

The applicant seeks agreement that the appropriate pathway for marketing approval of Iohexol Powder is a 505(b)(2) application. The applicant will rely on the safety and efficacy information previously referenced by the FDA in the approval of the oral indication for the listed drug. The applicant also plans to submit updated safety and efficacy information from the published literature in the new drug application (NDA).

The applicant believes that an abbreviated new drug application (ANDA) pathway for Iohexol Powder does not apply due to the narrowing of the indication for oral use only and because the proposed product is not identical in dosage form, strength, formulation and labeling to the listed drug and therefore is beyond the permissible changes allowed via suitability petitions.

*Does the FDA agree with the proposed 505(b)(2) regulatory pathway as well as the approach to providing updated safety and efficacy information in the NDA?*

### **FDA's Response 2:**

**A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by**

**Section 505(b)(2)” available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>)**

**If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature.**

**If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s)(which we consider to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that is the subject of an NDA approved under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.**

**We are unclear of the details of your proposed indication (see comments above); consequently, we cannot provide assurance that your plan for safety and efficacy information is sufficient. We anticipate that you could craft a proposed indication statement that could be supported by published literature.**

*Sponsor’s Question 3:*

Because the product will be indicated for oral use only, it will be provided as a nonsterile oral preparation. Instructions and precautionary statements will be provided to reinforce oral use only and to avoid product misuse. Furthermore, the unique primary package design ensures absolute differentiation from currently marketed products.

*Does the FDA agree that the product differentiation is sufficient to ensure appropriate clinical use of the nonsterile preparation of the product for oral use only?*

**FDA's Response 3:**

**Before addressing this question, we request clarification upon your indication and whether or not you plan to develop an injectable presentation of the drug. We encourage you to elaborate upon these items and the unique primary package design features at the upcoming meeting.**

**Chemistry, Manufacturing and Controls Questions**

*Sponsor's Question 4:*

The applicant intends to submit a Type II Drug Master File (DMF) for the drug substance. The DMF will describe the full chemistry, manufacturing and controls information required to support the final NDA and the product quality and control strategy will conform to the active pharmaceutical ingredient requirements for oral usage. Consequently, the Drug Substance section of the NDA will contain minimal information as most of the information will be contained in the referenced DMF.

*Does the FDA agree with this approach?*

**FDA's Response 4:**

**Yes.**

*Sponsor's Question 5:*

The <sup>(b) (4)</sup> for iohexol will be presented in the briefing package. It starts with <sup>(b) (4)</sup>

*Does the FDA agree that <sup>(b) (4)</sup> may be designated as regulatory starting materials?*

**FDA's Response 5:**

**Yes.**

*Sponsor's Question 6:*

The proposed specification for release of the drug substance is based on the USP monograph for iohexol.

*Does the FDA agree that the proposed drug substance specification is appropriate for release of the drug substance to support the manufacture of the to-be-marketed drug product?*

**FDA's Response 6:**

**Yes.**

*Sponsor's Question 7:*

The proposed specification for the drug product has been developed consistent with the ICH Q6A guidelines for powders intended for dissolution and use as oral liquids. The applicant understands that the acceptance criteria will be reviewed during the NDA assessment. However, the applicant is seeking concurrence from FDA that the quality attributes chosen for testing are sufficient for the NDA.

*Does the FDA agree that the proposed drug product specification is acceptable for release of the to-be-marketed drug product?*

**FDA's Response 7:**

**From a preliminary standpoint, yes. Acceptability will be determined during review of the NDA.**

*Sponsor's Question 8:*

The applicant seeks agreement that the proposed primary (formal) stability study program for the drug product, which is based on ICH Q1A guidelines, is suitable and adequate for the filing of an NDA. Since the drug product is the same as the drug substance, there will be adequate stability data available for the drug substance well beyond 12 months of real time testing. The applicant intends to submit six months room temperature and accelerated stability data for three representative batches of the drug product packaged in the proposed container closure system at the time of the NDA submission. The applicant will provide updates to the agency with results of the ongoing stability studies by mid-cycle of the review and will ensure that the stability data is submitted in electronic format with statistical analysis of all stability-indicating quality attributes.

*Does the FDA agree with this stability data submission plan?*

### **FDA's Response 8:**

**No. At the time of submission of the NDA, we expect 6 months of accelerated stability data and 12 months of long-term stability data.**

### **Request for Waiver of In Vivo Bioavailability or Bioequivalence**

#### *Sponsor's Question 9:*

The bioavailability or bioequivalence of Iohexol Powder is self-evident based on the criteria in 21 CFR 320.22 because the product administered to the patient is an oral solution. The solution administered contains the same active drug ingredient in the same concentration and dosage form as prepared solutions of the listed drug for oral use. Furthermore, Iohexol Powder contains no inactive ingredients or other change in formulation from the listed drug that may significantly affect local availability or absorption. Solutions prepared from Iohexol Powder are intended for local availability and do not target a clinical effect based on systemic availability which is very low.

The applicant will provide physicochemical data demonstrating the equivalence of prepared solutions for administration of Iohexol Powder compared with prepared solutions for administration of the listed drug to ensure similar local availability. Literature information will be provided to demonstrate the limited absorption of orally administered iohexol.

*Does the FDA support the applicant's request for a waiver from conducting in vivo bioavailability or bioequivalence studies based on the assumption that release of the drug substance from the drug product is self-evident?*

### **FDA's Response 9:**

**We are still reviewing this item and plan to provide feedback at the meeting or in a follow-up communication.**

### **Nonclinical Question**

#### *Sponsor's Question 10:*

The applicant seeks agreement that the safety of orally administered iohexol is considered adequately established to support approval of the proposed 505(b)(2) application for Iohexol Powder, to be administered orally for imaging opacification. The proposed drug product, when mixed with water or beverage for oral administration, is substantially equivalent to the previously approved and marketed iohexol listed drug, when prepared under similar conditions. Nonclinical information relating to the safety of oral administration of iohexol will be summarized and presented in the NDA, based on open literature publications available since the most recent label update for the listed drug product.

*Does the FDA agree, based on the previous approval of the iohexol listed drug product for oral administration, that no new nonclinical studies with Iohexol Powder are required to support approval of the proposed 505(b)(2) application?*

**FDA's Response 10:**

**It is unlikely that a new nonclinical study or studies would be required to support your 505(b)(2) application for Iohexol (b) (4) Oral Solution. However, if safety issues are identified during our review of your application, additional information and/or nonclinical studies may be requested.**

**Clinical Question**

*Sponsor's Question 11:*

The applicant seeks agreement that the safety and efficacy of orally administered iohexol is considered adequately established to support approval of the proposed 505(b)(2) application for Iohexol Powder, to be administered orally for imaging opacification. The proposed drug product, when mixed with water or beverage for oral administration, is substantially equivalent to the previously approved and marketed iohexol listed drug, prepared under similar conditions with minor differences in formulation. Since Iohexol Powder is intended for imaging opacification of the gastrointestinal tract, and since iohexol has minimal oral bioavailability, the applicant believes that new studies are not needed to re-establish iohexol's safety and effectiveness for oral use. Clinical information relating to the safety and efficacy of oral administration of iohexol will be summarized and presented in the NDA, based on open literature publications available since the most recent label update for the listed drug product.

*Does the FDA agree, based on the previous approval of the iohexol listed drug product for oral administration, that no new clinical studies with Iohexol Powder are required to support approval of the proposed 505(b)(2) application?*

**FDA's Response 11:**

**In principal we agree, assuming the proposed indication is consistent with oral use of Omnipaque. As noted above, please clarify the intended clinical use of your product. In addition, based on the indication, please conceptualize what will go into the clinical studies section of the label. We anticipate that you will also conduct an adequate literature review to support oral use of your product.**

## **Discussion**

The meeting began with a presentation by Otsuka. Otsuka stated that there wasn't a need to discuss questions 4-7 (CMC) questions since FDA agreed with Otsuka's proposals. In their presentation Otsuka commented on each of the responses from FDA except questions 4-7.

### Question 1

Otsuka commented that the product will only be used (b) (4) as an adjunct to CT imaging of the abdomen. (b) (4)

### Question 2

Otsuka stated that they (b) (4) in support of their 505(b)(2) application for Iohexol. FDA acknowledged that this proposal seemed reasonable.

### Question 3

Otsuka stated that their Iohexol product will be more concentrated than the marketed Omnipaque oral product. It will be packaged in a beverage type bottle with a screw off cap and a foil pouch as secondary packaging. Otsuka stated that the product will be clearly labeled "non sterile", (b) (4) and "for oral use only". Because FDA had expressed a concern about the product packaging and labeling, Otsuka asked if FDA wished to see the slides that described the labeling, packaging, and preparation for use of the product. FDA said that would be helpful. Otsuka then moved quickly to that portion of the presentation and explained how the product would be reconstituted, packaged, and labeled. After reviewing that portion of the presentation FDA commented that the portion on the presentation dedicated to the packaging, labeling, and reconstitution of the product had been helpful in clarifying product labeling and packaging issues.

FDA also commented that Otsuka's proposal for packaging and labeling of Iohexol seemed reasonable but because the chemistry reviewers could not be present at the meeting it was difficult to state unequivocally that the labeling and packaging were acceptable.

### Questions 4-7

FDA found Otsuka's approach to be acceptable.

### Question 8

Otsuka stated they plan to include the following stability data in the application when it is submitted: (1) 6 months of long term and 12 months of accelerated stability data on their first 3 primary batches, and (2) 12 months of long-term and 6 months of accelerated stability data for a supportive drug batch. FDA then commented that this information needed to be reviewed by the chemistry team because they had the expertise to ascertain whether or not the plan for submission of CMC data was sufficient or whether additional data was needed. FDA advised Otsuka to send this question to FDA as follow-up correspondence so that it could be addressed fully by the chemistry team.

### Question 9

Otsuka reiterated its proposal that FDA grant their Iohexol product a biowaiver primarily based on the criteria found in CFR 320.22(b)(3). Otsuka explained that their Iohexol product has no excipients, [REDACTED] <sup>(b) (4)</sup> is highly soluble in the liquid in which it is administered to the patient, has low systemic absorption, fast dissolution, and its structure is highly delineated.

### Question 10

Otsuka stated that if nonclinical issues are identified during the review of the application that FDA should permit Otsuka to address those issues postmarketing because of the marketing history and clinical safety profile of Iohexol. FDA stated that it could not guarantee that any preclinical safety issues identified during the review process could be delayed to the postmarketing period. FDA also stated that no safety issues have emerged that would require preclinical studies based on the clinical use of the product and does not anticipate safety issues emerging during the review. However, if safety issues are identified FDA will try to communicate any safety issues to Otsuka early in the review cycle.

### Question 11

FDA inquired of Otsuka what prompted Otsuka to propose marketing of Iohexol since Omnipaque was already marketed. Otsuka replied (1) their product is more palatable than Omnipaque (2) their product should reduce the likelihood of medication errors based on its packaging, labeling (3) the packaging makes it more convenient for patient use, and (4) Otsuka's Iohexol product provides more accurate dosing.

FDA inquired about Otsuka's plan for the package insert for their product, specifically the clinical trials section of the label. Otsuka replied that they had not finalized the information for this section of the label, but would send it to FDA for review prior to submission of the application if this was what FDA wanted. FDA responded that there was no need to send in a separate submission for FDA review and that the labeling should be included with the NDA when it is submitted.

FDA also inquired of Otsuka's plans for support of the efficacy claim for their product and asked if Otsuka planned to perform a meta-analysis. Otsuka replied there were no such plans.

Otsuka again reiterated that their product will not have a specific diagnostic claim but the indication statement will reflect that it will be used as an adjunct to the CT exam (b) (4)

Otsuka also stated that it will use literature in support of the safety and efficacy of its Iohexol product.

Otsuka was asked about the location for the manufacture of its Iohexol product and replied that the facilities involved in the manufacture of the drug product are located in the Czech Republic and in New York. According to Otsuka, Interpharma Praha in the Czech Republic will manufacture the drug substance (b) (4) by Ultra Seal Corporation at their facility in New Paltz, New York. (b) (4)

### Summary

Questions 3, 8, and 9 were not fully addressed at the meeting because the chemistry team could not be present. FDA encouraged Otsuka Pharmaceuticals to resubmit those questions to the Division through the Project Manager who would convey them to the chemistry team to provide complete responses. Question 3 addressed labeling differentiation, question 8, product stability, and question 9, a request for a BA/BE Waiver for the Otsuka product.

The minutes were prepared by James Moore, Regulatory Health Project Manager.

James Moore, PharmD., M.A.  
Regulatory Health Project Manager

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