

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203794Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **203794**

SUPPL # **N/A**

HFD # **170**

Trade Name: **Nucynta**

Generic Name: **tapentadol oral solution**

Applicant Name: **Janssen Pharmaceuticals, Inc.**

Approval Date, If Known: **October 15, 2012**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

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

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

No clinical data was reviewed to support this submission. The applicant obtained a biowaiver.

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

N/A

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?

N/A

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).

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: Dominic Chiapperino, Ph.D.
Title: Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products
Date: October 15, 2012

Name of Office/Division Director signing form: Sharon Hertz, M.D.
Title: Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products

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

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

/s/

DOMINIC CHIAPPERINO
10/15/2012

SHARON H HERTZ
10/15/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203794	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Nucynta Established/Proper Name: tapentadol Dosage Form: oral solution, 20 mg/mL		Applicant: Janssen Pharmaceuticals, Inc Agent for Applicant (if applicable): Janssen Research & Development, LLC
RPM: Dominic Chiapperino, Ph.D. Senior Regulatory Health Project Manager		Division: Division of Anesthesia, Analgesia, and Addiction Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not reply upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 15, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

<p>❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received n/a</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><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</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments: New oral solution formulation, no special characteristics</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates n/a</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No n/a</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

³ 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.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes n/a If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes n/a If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes n/a If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified n/a 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire n/a
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified n/a

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

n/a

Yes No

Yes No

Yes No

Yes No

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Final as of 10/23/12
Officer/Employee List	
❖ 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
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	AP, 10/15/12
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Final, submitted 10/15/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Submitted 12/15/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Final, submitted 10/15/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Submitted 12/15/12
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Submitted 8/3/12 (same as approved)
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	n/a, "Nucynta" already approved proprietary name for immediate-release tablets; both Nucynta tablets and oral solution will be marketed as "immediate-release" formulations of "Nucynta" (tapentadol)
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM (Chiapperino, 10/15/12) <input checked="" type="checkbox"/> DMEPA (Holquist email, 7/12/12; Baugh, 7/11/12) <input checked="" type="checkbox"/> DMPP/PLT (Mills, 9/20/12) <input checked="" type="checkbox"/> ODPD (DDMAC) (Toombs, 9/28/12; Chung-Davies, 9/20/12) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	Filing reviews/memos: Chiapperino, 10/11/12 Emami, 4/19/12 Lee, 2/27/12 Moore, 2/24/12 Riviere, 2/24/12 Riley, 1/18/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2) n/a
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) n/a
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included Hertz, 10/15/12
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<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"> • Date reviewed by PeRC <u>8/8/12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Reverse chronology: Information Request (IR) emails on 10/10/12, 8/21/12, 8/9/12, 7/12/12 (2), 6/13/12, 6/6/12, 5/15/12, 4/25/12/20/12; DR letter, 3/8/12; IR email, 3/2/12; Filing letter, 2/27/12
❖ Internal memoranda, telecons, etc.	none
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg Included copy of written responses excerpted from FDA email
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	none
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ 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>)	Hertz, 10/15/12
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>)	Two included, for 1937-1 and 1937-2 as shown in AP letter
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	none
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	none

⁶ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None n/a
<ul style="list-style-type: none"> Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	No clinical studies needed to support approval
<ul style="list-style-type: none"> Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	Lerner, 9/7/12
<ul style="list-style-type: none"> Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) 	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Clinical Microbiology Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> Statistical Division Director Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Statistical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Statistical Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None Xu co-signed Lee review
<ul style="list-style-type: none"> Clinical Pharmacology review(s) (<i>indicate date for each review</i>) 	8/21/12
<ul style="list-style-type: none"> DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>) 	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
<ul style="list-style-type: none"> Pharmacology/Toxicology Discipline Reviews 	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None Wasserman co-signed Emami review
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	Emami, 8/15/12
<ul style="list-style-type: none"> Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> ECAC/CAC report/memo of meeting 	<input checked="" type="checkbox"/> None Included in P/T review, page
<ul style="list-style-type: none"> DSI Nonclinical Inspection Review Summary (<i>include copies of DSI 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"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None Peri co-signed Bertha reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		Bertha, 8/14/12; Bertha, 4/25/12; Bertha, 2/14/12
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		Riley, 8/7/12; Riley, 6/5/12; Riley, 4/19/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input 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>		Documented as acceptable in Bertha review dated 2/14/12, pages 43-44
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		n/a
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		n/a
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: 9/18/12memo <input checked="" type="checkbox"/> Acceptable Bertha memo, 9/20/12 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (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 type="checkbox"/> Not needed (per review)

⁷ 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

DOMINIC CHIAPPERINO
10/23/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, October 10, 2012 3:19 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: NDA 203794, Information Request - labeling revisions
Attachments: Nucynta oral solution FDA tracked change PI 10-10-12.pdf; Nucynta oral solution FDA PI 10-10-12 CLEAN.doc; Nucynta oral solution FDA MG 10-10-12 CLEAN.doc; Nucynta oral solution FDA IFU 10-10-12 CLEAN.doc

Hi Peggy,

Referring to NDA 203794 for Nucynta oral solution, we have the following comments and recommended revisions concerning the package insert, Medication Guide, and Instructions for Use:

1. Regarding the package insert, please find the attached pdf file that shows most FDA revisions in tracked-change format relative to the labeling you submitted on August 29, 2012. A clean Word version of this file is also included, which contains all FDA revisions shown in the tracked-change file plus one further revision to section (now) 2.7 Instructions for Use to reflect that the patient Instructions for Use are not considered part of the Medication Guide. The IFU is separate patient labeling.
2. Regarding the Medication Guide and the patient Instructions for Use, FDA recommended revisions are substantial and only clean versions of these as separate Word format files are attached.
3. For the IFU, we have the following additional comments:

a. Note the revised text:

- You will be provided (See Figure A.):
 - 1 bottle of NUCYNTA® oral solution
 - 1 oral syringe
 - 1 adaptor

You should label the figure below this text as "Figure A", and revise all figure references below this point with sequential lettering. The label in Figure A for (b) (4) should be modified to "oral syringe" and this term should be used consistently throughout the IFU. Likewise, the label (b) (4) should be modified to "adaptor".

b. Placement of the figures should be adjacent to or just below the relevant text, as with Figure A.

c. For what will be labeled Figure C (as referenced in the text), the ribbed end of the adaptor in Figure C should be labeled as such.

d. For the following text...

To prepare a dose of NUCYNTA® oral solution:

1. Hold the oral syringe in one hand. With your other hand, fully push down (depress) the plunger (See Figure D).

... a figure should be inserted (as Figure D) that conveys these instructions.

e. Figure G (formerly Figure 5) should be revised to depict the bottle turned up-right and on a flat

surface. Currently, it looks like the person is holding the bottle in the air.

Please contact me if you have questions about FDA's labeling recommendations.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
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10903 New Hampshire Avenue
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69 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DOMINIC CHIAPPERINO
10/10/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, August 21, 2012 12:53 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: RE: Nucynta oral solution syringe

Dear Peggy,

Regarding the cumulative information now submitted to NDA 203794 for the new proposed dosing syringe, we have the following comments.

The proposed dosing device submitted for Nucynta Oral Solution has been found to be error-prone and is, therefore, unacceptable. Specifically, the graduations are in milligrams instead of milliliters, which is the traditional metric used on oral syringes and with which the medical community is familiar. Our most recent post-marketing experience is with an approved oral suspension where the device was graduated in milligrams and dosing errors occurred as a result (see link).

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm183649.htm>

Also, since we anticipate that Nucynta Oral Solution may be approved in the pediatric population, our concerns with this dosing device as proposed are heightened. We request that you re-design the oral syringe to be graduated in milliliters to avoid these kinds of errors.

Please contact me if you have questions.

Kind regards,

Dominic

Dominic Chiapperino, Ph.D.
*Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
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DOMINIC CHIAPPERINO
08/21/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, August 09, 2012 8:23 AM
To: 'Ferrone, Peggy [JRDUS]'
Subject: RE: Nucynta oral solution syringe

Hi Peggy,

We have one additional comment regarding the dosing syringe.

You indicated in the June 18, 2012 amendment, that the dosing accuracy of the new oral syringe is equivalent to the previous version. Provide confirmation that you will apply the same dosing accuracy acceptance criterion of [REDACTED] to the new syringe that was agreed to be applied for the acceptance of the previous syringe. Revise the oral syringe specification accordingly and submit it to the application.

Thank you, and kind regards,
Dominic

From: Ferrone, Peggy [JRDUS] [mailto:PFERRONE@its.jnj.com]
Sent: Friday, August 03, 2012 1:06 PM
To: Chiapperino, Dominic
Cc: Hillmer, Tania [JRDUS]
Subject: RE: Nucynta oral solution syringe

Hi Dominic,

Our Nucynta Oral Solution NDA 203794 response has been submitted via the Gateway. For your reference, attached is a copy of the cover letter and the CMC response document.

Regards,
Peggy

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/s/

DOMINIC CHIAPPERINO
08/09/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, June 13, 2012 10:31 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: Nucynta labeling, Information Request

Dear Peggy,

We refer you to tapentadol NDAs, NDA 200533 for Nucynta ER extended-release oral tablets, NDA 022304 for Nucynta immediate-release oral tablets, and pending NDA 203794 for Nucynta oral solution. We note the labeling revisions agreed upon for Nucynta ER and submitted April 18, 2012, as amendment to pending labeling/REMS supplement, sNDA 200533/S-002. Based on our review of multiple pending labeling supplements for NDA 022304 and proposed labeling for pending NDA 203794 for Nucynta oral solution, we have the following comments and request for revised proposed labeling for Nucynta immediate-release oral tablets and Nucynta oral solution:

(b) (4)

2) Regarding pending NDA 203794 for Nucynta oral solution, submit an amendment including, in Word format, a revised package insert and Medication Guide that address the following:

- a. Revise the package insert and Medication Guide to make both specific for Nucynta oral solution rather than as common labeling with Nucynta immediate-release oral tablets. In view of our request to discontinue the Medication Guide for Nucynta immediate-release oral tablets, it is not appropriate nor practicable for Nucynta oral tablets and oral solution to have common product labeling when a Medication Guide is required only for the oral solution.
- b. Revise the package insert to make the labeling consistent with revisions made to Nucynta ER product labeling (as submitted April 18, 2012) for such sections of the Nucynta oral solution package insert that can or should have language common for all tapentadol product labeling.
- c. Revise the Medication Guide for Nucynta oral solution to better address concerns of overdosage and medication errors in dispensing and administering 20 mg/mL tapentadol oral solution. We refer you to approved Medication Guides for other concentrated opioid oral solutions, e.g. morphine sulfate oral solution, 100 mg/5 mL (NDA 201517) or oxycodone hydrochloride oral solution, 100 mg/ 5 mL (NDA 200535) . Note that the concerns warranting the Medication Guide for Nucynta oral solution are different and distinct from the concerns warranting a Medication Guide for Nucynta ER extended-release oral tablets and other extended-release/long-acting (ER/LA) opioids. Therefore, the Nucynta oral solution Medication Guide need not adhere to the draft one-page Medication Guide format and content discussed for Nucynta ER under the ER/LA class REMS. The morphine sulfate or oxycodone hydrochloride oral solution Medication Guides mentioned above would be the better model for Nucynta oral solution, and you may include such content specific and appropriate for tapentadol.

We will resume our review of product labeling for Nucynta immediate-release oral tablets and Nucynta oral solution once we have received the above requested amendments.

Please contact me if you have any questions.

Kind regards,

Dominic

Dominic Chiapperino, Ph.D.
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/s/

DOMINIC CHIAPPERINO
06/13/2012

From: [Holquist, Carol A](#)
To: [Fields, Ellen](#); [Baugh, Denise](#)
Cc: [Merchant, Lubna](#); [Chiapperino, Dominic](#); [Taylor, Kellie](#)
Subject: Re: DMEPA comments for Nucynt oral solution
Date: Thursday, July 12, 2012 2:16:29 PM

Ellen

I would prefer to have just the mg per mL on the label. This was my misunderstanding that the usual dose was 5 mL. Sorry for the confusion.

Carol

From: Fields, Ellen
Sent: Thursday, July 12, 2012 11:12 AM
To: Baugh, Denise
Cc: Merchant, Lubna; Holquist, Carol A; Chiapperino, Dominic
Subject: DMEPA comments for Nucynt oral solution

Hi Denise,

Thank you so much for the review of the Nucynta oral solution labels and packaging. I have one question. One of your recommendations is as follows:

Revise the statement of strength from "20 mg/mL" to read "100 mg/5 mL" to maintain consistency with other approved oral solutions and to minimize the potential for medication errors due to miscalculations. Please note that there should be space between the number and the metric measurement.

For the relatively recent approvals of Oxycodone and Morphine oral solutions, the container and label include both the mg/ml and mg/5 ml concentrations as shown below:

In order to be consistent we thought it would be appropriate to recommend to the Sponsor to include both concentrations, as in the oxycodone and morphine labels. Would you have any objection to that?

Thanks for your help!

Ellen

Ellen Fields, M.D., M.P.H.

Clinical Team Leader

DAAAP

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/s/

LUBNA A MERCHANT on behalf of DENISE V BAUGH
10/15/2012

LUBNA A MERCHANT
10/15/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, July 12, 2012 2:57 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: RE: NDA 203794, Information Request, labeling and dosing syringe

Hi Peggy,

We have some additional internal discussion and realize that our comments # 1 and 2 in my previous email should now be disregarded. Given the recommended dosing of 50, 75 or 100 mg of Nucynta every 4 to 6 hours, there is no added benefit or clarity in emphasizing "100 mg/5 mL" for the oral solution versus its unit concentration of "20 mg/mL".

Please respond only to Comments 3 through 8 below.

Thank you,
Dominic

From: Chiapperino, Dominic
Sent: Thursday, July 12, 2012 1:36 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: NDA 203794, Information Request, labeling and dosing syringe

Dear Peggy,

Regarding your NDA 203794 for Nucynta oral solution, we have reviewed your recent amendments containing proposal of a new dosing syringe and limited information about the new syringe. We have the following comments at this time, along with comments about your proposed Carton and Container labeling, as follows:

Container Label and Carton Labeling (100 mL and 200 mL bottle)

(b) (4)

Proposed Dosing Device

5. Revise the statement, [REDACTED] (b) (4) to read "For Use Only with Nucynta Oral Solution".
6. Provide details of the process for replacing lost syringes and syringe adaptors and how this process will be communicated to patients and pharmacists.
7. [REDACTED] (b) (4)

8. Submit with your amendment all of the supporting CMC-related information both for the syringe and the adapter (e.g., specifications, materials of construction, qualification test results, compliance with food contact regulations).

Please let me know if you have any questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
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FDA, Center for Drug Evaluation and Research
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DOMINIC CHIAPPERINO
07/18/2012
Archiving email follow-up, 7/12/12

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Wednesday, June 06, 2012 10:05 AM
To: 'pferrone@its.jnj.com'
Subject: RE: NDA 203794 Information Request

Dear Ms. Ferrone

We are reviewing the Microbiology section of your submission for NDA 203794. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). An attribute listed in the drug product specifications must be assessed for each lot of drug product at release by performing the appropriate test procedure. Therefore, the proposal to use skip lot testing for microbial limits should be withdrawn from your application.

However, after obtaining sufficient manufacturing experience and acceptable microbial limits testing data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release. After approval of omitting microbial limits testing from the release specification, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.

Please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you,

*Khushboo Sharma, MBA, RAC
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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KHUSHBOO SHARMA
06/06/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, May 15, 2012 1:00 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: NDA 203794, Information Request, dosing device

Dear Peggy,

Referring to NDA 203794 for Nucynta oral solution, DMEPA has evaluated your proposed dosing syringe and has the following comments and request for additional information and/or proposal of a different dosing device, as follows:



Contact me if you have any questions.

Thank you, and best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
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Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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DOMINIC CHIAPPERINO
05/15/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Wednesday, April 25, 2012 11:04 AM
To: 'pferrone@its.jnj.com'
Subject: RE: NDA 203794 Information Request

Dear Ms. Ferrone

We are reviewing the CMC section of your submission for NDA 203794. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

We acknowledge your responses to comments 2 and 5 of our March 8, 2012, letter, which address the dose content uniformity and dosing accuracy that is achieved with the supplied dosing syringe (b) (4). As you have stated that the dosing syringe is to be used to ensure accurate dosing, we consider it to be an integral part of the drug product and had asked that you follow ICH Q6A recommendations performing content uniformity testing with this device. We have considered your proposal to indirectly assure content uniformity of doses by the dosing accuracy requirements applied to the dosing syringe, the dosing accuracy study data that you have provided, the requirements for dosing accuracy put in place by the syringe manufacturer, and we have consulted our clinical team regarding their dosing accuracy expectations. Revise the proposed dosing accuracy acceptance criterion in the syringe specification to (b) (4). Specific testing of content uniformity with the dosing (b) (4) as part of the drug product specification would then not be necessary.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you,

*Khushboo Sharma, MBA, RAC
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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KHUSHBOO SHARMA
04/25/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Friday, April 20, 2012 1:12 PM
To: 'pferrone@its.jnj.com'
Subject: NDA 203794 Information Request

Dear Ms. Ferrone

We are reviewing the Microbiology section of your submission for NDA 203794. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1. The drug product microbiological specifications should clearly identify the acceptance criteria both for enumeration and specific microorganisms. Merely stating that the drug product meets Current USP <1111> is not sufficient.
2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the *Burkholderia cepacia* complex. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.
3. Your proposal to perform skip lot testing for the Microbial Limits test is unacceptable because it does not comply with 21 CFR 211.165(a) and (b). Microbial limits testing should be performed on each lot of drug product at release. After obtaining sufficient data to demonstrate control of drug product bioburden, you may submit a prior approval supplement proposing to omit finished product microbial limits testing for batch release. After approval of omitting microbial limits testing at release, microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you,

Khushboo Sharma, MBA, RAC
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
04/20/2012

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM (Mike Wade, Olga Salis, and Becki Vogt), Mathilda Fienkeng, and LaToya (Sheneé) Toombs

FROM: (Name/Title, Office/Division/Phone number of requestor)
**Division of Anesthesia, Analgesia, and Addiction Products
Dr. Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D.,
Senior Regulatory Health Project Manager, 301-796-1183**

REQUEST DATE
Mar. 23, 2012

IND NO.

NDA/BLA NO.
NDA 203794

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW) **Original NDA, labeling**

NAME OF DRUG
Nucynta (tapentadol) Oral Solution, 20 mg/mL

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
3 (new formulation)

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)
Aug. 2, 2012

NAME OF FIRM:
Janssen Pharmaceuticals, Inc

PDUFA Date: **Oct. 15, 2012**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission: <\\CDSESUBI\EVSPROD\NDA203794\203794.enx> (Dec. 15, 2011 submission)

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Note: The labeling for this product will be common labeling with already-approved labeling for Nucynta immediate-release oral tablets (NDA 022304).

Mid-Cycle Meeting: May 10, 2012
Other Team Meetings: April 17, June 14, and July 17, 2012
Labeling Meetings: June 6 and July 10, 2012
Wrap-Up Meeting: August 9, 2012

SIGNATURE OF REQUESTER **Dominic Chiapperino (electronically signed)**

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

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/s/

DOMINIC CHIAPPERINO
03/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Division of Medical Policy Programs/Patient Labeling Team ATTN: Chris Wheeler, Carol A. McAlman		FROM: Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183		
DATE Mar. 23, 2012	IND NO.	NDA NO. 203794	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT Recvd. Dec. 15, 2011
NAME OF DRUG Nucynta (tapentadol) oral solution, 20 mg/mL		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 3	DESIRED COMPLETION DATE July 15, 2012
NAME OF FIRM: Janssen Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DAAAP received this new original NDA 203794 (10 month PDUFA clock, PDUFA date 10/15/12) for an oral solution of Nucynta that will have common labeling with the approved NDA 022304 for Nucynta (tapentadol) immediate-release oral tablets. We are requesting a consult review by PLT because there have been some revisions to the Medication Guide approved for NDA 022304 and proposed for NDA 203794 to add information related to the oral solution formulation under NDA 203794. SCPI will be provided by the review team as soon as it is available. NDA 203794 is fully electronic (eCTD format) and all files can be found in EDR, direct link: \\CDSESUB1\EVSPROD\NDA203794\203794.ENX All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Health Project Manager.				
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

DOMINIC CHIAPPERINO
03/23/2012



NDA 203794

DISCIPLINE REVIEW LETTER

Janssen Research & Development, L.L.C.
US Agent: Janssen Pharmaceuticals, Inc.
920 Route 202 PO Box 300
Raritan, New Jersey 08869

Attention: Peggy Ferrone
Manager, Regulatory Affairs

Dear Ms. Ferrone:

Please refer to your December 15, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta (tapentadol) oral solution, 20 mg/mL.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies:

1. With regard to the Raspberry Flavor (b) (4) received from (b) (4) to be used in the product formulation, perform an identity test for acceptance that has sufficient specificity (21 CFR 211.184(d)(2)) and establish a suitable reference material for comparison purposes (e.g., chromatographic profile comparison, spectral comparison).
2. The instructions for use of the drug product specifically and only call for the use of the provided oral syringe. You have stated in P.2.4 that this will “ensure accurate dosing.” As such, the oral syringe is considered an integral part of the drug product contrary to what you have stated in P.2.4. Revise the drug product specification to include, as recommended in ICH Q6A, a test for the content uniformity using the oral syringe that is supplied with the drug product.
3. Provide the method validation report AD-MVR-R331333-F041-LIQ-LC-004173-v1 that is said to support the HPLC method LC- (b) (4) used for determination of identity, assay, and degradants for the 20 mg/mL strength drug product. This report could not be located in the application. In addition provide the corresponding method that is used for the determination of identity, assay, and degradants for the (b) (4) strength drug product.
4. Provide clarification and additional information to specifically identify the dosing syringe that is supplied by (b) (4). The P.2 section of the application shows a (b) (4) syringe (b) (4) whereas the P.7 section describes the syringe as having a nominal volume of (b) (4). The letter of authorization for DMF (b) (4) does not

specify the syringe that they are providing for your application either. Lastly, the composition of the component parts of the syringe listed in Table 3 of the P.7 section is not consistent with the raw materials that are said to be used in the DMF.

5. Revise the specification for the dosing syringe to include an acceptance test and acceptance criteria for deliverable volume. Volume error should not be greater than (b) (4) from the calibrated target amounts.
6. Revise the post approval stability protocols for the commitment and annual batches to indicate that the samples will be stored in a horizontal position.

We have determined that the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
03/08/2012

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, March 02, 2012 3:39 PM
To: 'Ferrone, Peggy [JRDUS]'
Subject: NDA 203794, Information Request

Dear Peggy:

Please refer to your New Drug Application (NDA) for Nucynta (tapentadol) oral solution, 20 mg/mL.

We also refer to your amendment received on February 7, 2012, containing the clinical study report for relative bioavailability study HP5503/59; R331333PAI1044, "A relative bioavailability trial to compare a new tapentadol oral solution 100 mg with the tapentadol immediate-release 100 mg tablet."

In the interest of having complete information concerning the above study, we request that you submit the following information:

1. Regarding study HP5503/59, confirm that:
 - a. the tapentadol oral solution used in the study is the to-be-marketed formulation; and
 - b. the FDA-approved Nucynta (tapentadol) immediate-release tablet was the immediate-release tablet formulation used as reference.
2. In addition to submitted Bioanalytical Analyses Study SBA_S_09040 (i.e., study PK1210A), and in order to have complete information concerning bioanalytical analyses, submit the following reports:
 - a. PK1134, "Complete Validation of an LC-MS/MS method for the determination of R331333 and R403347 in human serum," December 2007, including also Amendment 1 to study report PK1134, January 2009, containing long-term (24 months) stability data at -25°C [REDACTED] (b) (4)
 - b. PK1070 (SBA_S_07093), "Partial validation of a method for the determination of CG5503 free base and its metabolite CG5503 glucuronide (GRTE1472) in human serum by LC-MS/MS," including also Amendment 1 to report SBA_S_07093, 2008, containing freeze/thaw stability data (-25°C/room temperature) and short-term (72 hours) stability data at room temperature [REDACTED] (b) (4) respectively); and
 - c. PK711 (SBA_S_04004), "Stability of CG5503, CG5503 glucuronide (GRTE1472), and CG5503 sulfate (GRT3793H) in human blood and human serum - investigation by LC-MS/MS," October 2007, containing post-preparative stability data, 192 hours at 8°C (conditions during autosampling) [REDACTED] (b) (4)

If you have any questions please contact me.

Sincerely,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
03/02/2012



NDA 203794

FILING COMMUNICATION

Janssen Research & Development, L.L.C.
on behalf of Janssen Pharmaceuticals, Inc.
920 Route 202 PO Box 300
Raritan, New Jersey 08869

Attention: Peggy Ferrone
Manager, Regulatory Affairs

Dear Ms. Ferrone:

Please refer to your New Drug Application (NDA) dated and received December 15, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Nucynta (tapentadol) oral solution, 20 mg/mL.

We also acknowledge receipt of your amendment dated February 7, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 15, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 21, 2012.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SHARON H HERTZ
02/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: <i>(Division/Office)</i> Bryan Riley, Ph.D., Acting Team Leader, New Drug Microbiology Staff (OPS)			FROM: Craig Bertha, Ph.D., DNDQA3/Branch 8	
DATE 17-JAN-2012	IND NO. N/A	NDA NO. N203794	TYPE OF DOCUMENT Original NDA [505(b)(1)]	DATE OF DOCUMENT 15-DEC-2012
NAME OF DRUG Nucynta (tapentadol) oral solution		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE 15-APR-2012
NAME OF FIRM: Janssen Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT		RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW X OTHER <i>(Specify below)</i>
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER			CHEMISTRY PHARMACOLOGY BIOPHARMACEUTICS OTHER	
III. BIOPHARMACEUTICS				
DISSOLUTION BIOAVAILABILITY STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS <i>IN-VIVO</i> WAIVER REQUEST	
IV. DRUG EXPERIENCE				
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS <i>(List below)</i> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
CLINICAL			PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the microbiological aspects of the application. The drug product specification includes testing as per USP <61> and <62> and application of the USP <1111> acceptance criteria. No preservative is used in the formulation, but the applicant claims that the tapentadol HCl drug substance has antimicrobial activity (see P.2.5). Also, in P.5.6, the applicant proposes skip lot testing for the microbiological purity. The application is in the EDR.				
cc: Orig. NDA # 203794 ONDQA/DIV3/CBertha ONDQA/DIV3/PPeri OPS/JMcVey OND/DAAP/DChiapperino ONDQA/DIV3/DChristodoulou OND/DAAP/SPatwardhan				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY <i>(Check one)</i> MAIL HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

CRAIG M BERTHA
01/17/2012

PRASAD PERI
01/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST		
TO (Division/Office): New Drug Microbiology Staff <i>E-mail to: CDER OPS IO MICRO</i> <i>Paper mail to: WO Bldg 51, Room 4193</i>		FROM: Swati Patwardhan 301-796-4085 PROJECT MANAGER (if other than sender):		
REQUEST DATE 1/6/2012	IND NO.	NDA NO.203794	TYPE OF DOCUMENTS-000	DATE OF DOCUMENT 12/15/2011
NAMES OF DRUG NUCYNTA® (tapentadol) Oral Solution		PRIORITY CONSIDERATION Standard	PDUFA DATE 10/15/2012	DESIRED COMPLETION DATE 8/15/2012
NAME OF APPLICANT OR SPONSOR: Janssen Pharmaceuticals				
GENERAL PROVISIONS IN APPLICATION				
<input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED <input type="checkbox"/> CBE-0 SUPPLEMENT <input checked="" type="checkbox"/> NDA FILING REVIEW NEEDED BY: <u>2/15/2012</u> <input type="checkbox"/> CBE-30 SUPPLEMENT <input type="checkbox"/> BUNDLED <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY <input type="checkbox"/> PA Supplement <input type="checkbox"/> DOCUMENT IN EDR				
COMMENTS / SPECIAL INSTRUCTIONS: NDA 203794, NUCYNTA® (tapentadol) Oral Solution, is for the management of moderate to severe acute pain. Request microbiology input for controls of this aqueous non-sterile formulation and B. Cepacea testing. EDR: \\cdsesub1\EVSPROD\NDA203794\0000				
SIGNATURE OF REQUESTER: Swati Patwardhan		REVIEW REQUEST DELIVERED BY (Check one):		
		<input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> EDR <input type="checkbox"/> E-MAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
		DOCUMENTS FOR REVIEW DELIVERED BY (Check one):		
		<input checked="" type="checkbox"/> EDR <input type="checkbox"/> E-MAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		

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/s/

SWATI A PATWARDHAN
01/06/2012

REQUEST FOR CONSULTATION

TO (Office/Division):
Controlled Substance Staff (CSS, HFD-009)
ATTN: Corinne Moody, Sandra Saltz

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Anesthesia, Analgesia, and Addiction Products;
Bob A. Rappaport, M.D., Director
Point-of-contact: Dominic Chiapperino, Ph.D., Senior
Regulatory Health Project Manager, 301-796-1183

DATE
Dec. 27, 2011

IND NO.

NDA NO.
203794

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
recvd: Dec. 15, 2011

NAME OF DRUG
Nucynta (tapentadol) Oral
Solution

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG
3

DESIRED COMPLETION DATE
July 15, 2012

NAME OF FIRM: Janssen Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: **DAAAP received this new NDA (10 month PDUFA clock) for a new formulation of tapentadol, an oral solution, but same indication as for the immediate-release approved tapentadol product, Nucynta/NDA 022304, "Relief of moderate to severe acute pain in patients 18 years of age or older." We are requesting consult review by CSS for abuse liability perspective.**

NDA 203794 is fully electronic (eCTD format) and all files can be found in EDR, direct link:

\\CDSESUB1\EVSPROD\NDA203794\203794.ENX

All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Health Project Manager.

SIGNATURE OF REQUESTOR
Dominic Chiapperino (electronically signed)

METHOD OF DELIVERY (Check one)
 DARRTS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

DOMINIC CHIAPPERINO
12/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Office of Surveillance and Epidemiology ATTN: Danyal Chaudhry, Safety Regulatory Project Manager		FROM: Division of Anesthesia, Analgesia, and Addiction Products – Bob A. Rappaport, M.D., Director Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, 301-796-1183		
DATE Dec. 27, 2011	IND NO.	NDA NO. 203794	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT Recvd. Dec. 15, 2011
NAME OF DRUG Nucynta (tapentadol) Oral Solution		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG Type 3	DESIRED COMPLETION DATE July 15, 2012
NAME OF FIRM: Janssen Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: DAAAP received this new NDA (10 month PDUFA clock) for a new formulation of tapentadol, an oral solution, but same indication as for the immediate-release approved tapentadol product, Nucynta/NDA 022304, "Relief of moderate to severe acute pain in patients 18 years of age or older." We are requesting: <ul style="list-style-type: none"> • DMEPA review of Package Insert, Medication Guide, and C&C labeling • (Optional) DPV review of adverse reactions, warnings and precautions sections to see if updates in Package Insert warranted based on AERS cases for approved tapentadol products Nucynta and Nucynta ER. NDA 203794 is fully electronic (eCTD format) and all files can be found in EDR, direct link: \CDSESUB1\EVSPROD\NDA203794\203794.ENX All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Health Project Manager.				
SIGNATURE OF REQUESTER Dominic Chiapperino (signed electronically)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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