

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**200533Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 200533	
		NAME OF APPLICANT/NDA HOLDER Ortho-McNeil-Janssen Pharmaceuticals, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) NUCYNTA™ ER			
ACTIVE INGREDIENT(S) Tapentadol HCl		STRENGTH(S) 50mg, 100mg, 150mg, 200mg, 250mg	
DOSAGE FORM Extended Release Tablets			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number RE 39,593E (Reissue of US 6,248,737)		b. Issue Date of Patent See attached page	c. Expiration Date of Patent June 18, 2018
d. Name of Patent Owner Grunenthal GmbH		Address (of Patent Owner) Zieglerstr. 6, 52078	
		City/State Aachen	
		ZIP Code Germany 52078	FAX Number (if available) 49 241 569 2655
		Telephone Number 49 241 569 2590	E-Mail Address (if available) patents@grunenthal.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.) Crowell & Morning, P.O. Box 14300	
		City/State Washington, D.C.	
		ZIP Code 20044-4300	FAX Number (if available) 202-628-8844
Joseph D. Evans		Telephone Number 202-624-2500	E-Mail Address (if available) jdevsans@crowell.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
 Applicant understands question 2.2 to be asking whether the patent claims only the form of the active ingredient described in the approved application. The patent claims the form of the active ingredient described in the approved NDA, among others, and accordingly is appropriately submitted for listing.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) See attached page	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Relief of moderate to severe chronic pain, in accordance with approved labeling, including, for example, the Indications and Usage and Dosage and Administration sections.
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**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6: Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



10/28/09

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Joseph S. Kentoffio	
Address Johnson & Johnson One Johnson & Johnson Plaza	City/State New Brunswick, NJ
ZIP Code 08933	Telephone Number (732) 524-3711
FAX Number (if available) (732) 524-5008	E-Mail Address (if available) jkentoff@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**ATTACHED PAGE 1**

**US Patent No. RE 39,593E**

**1b Issue Date of Patent**

**April 24, 2007**

**(US 6,248,737 issued June 19, 2001)**

**4.2 Patent Claim Number(s) (as listed in the patent)**

**8, 86, 88, 90, 91, 93, 94, 95, 96, 98, 100, 101, 103, 105, 106, 108, 110, 112,  
114, 117, 136, 137, 138, 140**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER 200533	
		NAME OF APPLICANT/NDA HOLDER Ortho-McNeil-Janssen Pharmaceuticals, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) NUCYNTA™ ER			
ACTIVE INGREDIENT(S) Tapentadol HCl		STRENGTH(S) 50mg, 100mg, 150mg, 200mg, 250mg	
DOSAGE FORM Extended Release Tablets			
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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number US 6,071,970		b. Issue Date of Patent 06/06/2000	c. Expiration Date of Patent June 6, 2017
d. Name of Patent Owner NPS Pharmaceuticals Inc.		Address (of Patent Owner) 550 Hills Drive	
		City/State Bedminster, New Jersey	
		ZIP Code 07921	FAX Number (if available) (908) 450-5351
		Telephone Number (908) 450-5300	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  Edward Stratemeier		Address (of agent or representative named in 1.e.) NPS Pharmaceuticals, 550 Hills Drive	
		City/State Bedminster, New Jersey	
		ZIP Code 07921	FAX Number (if available)
		Telephone Number (908) 450-5305	E-Mail Address (if available) estratemeier@nps.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No	

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
118	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Relief of moderate to severe chronic pain, in accordance with approved labeling, including, for example, the Indications and Usage and Dosage and Administration sections.
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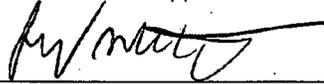
**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)** **Date Signed**  
 10/28/09

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<b>Name</b> Joseph S. Kentoffio	
<b>Address</b> Johnson & Johnson One Johnson & Johnson Plaza	<b>City/State</b> New Brunswick, NJ
<b>ZIP Code</b> 08933	<b>Telephone Number</b> (732) 524-3711
<b>FAX Number (if available)</b> (732) 524-5008	<b>E-Mail Address (if available)</b> jkentoff@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

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- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
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- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # **200533**

SUPPL # **N/A**

HFD # **170**

Trade Name: **Nucynta ER**

Generic Name: **tapentadol**

Applicant Name: **Janssen Pharmaceuticals, Inc. (c/o Johnson & Johnson Product Research and Development, LLC)**

Approval Date, If Known: **August 25, 2011**

### **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)**

b) 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.

**N/A**

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**

c) Did the applicant request exclusivity?

YES  NO

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

**Three**

d) 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).

NDA# 022304

Nucynta (tapentadol) immediate-release oral tablets, 50, 75, and 100 mg

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.)

N/A YES  NO

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

N/A

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:

N/A

(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:

N/A

(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:

N/A

(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:

**Investigation #1: Study R331333-PAI-3011: A Randomized, Double-Blind, Placebo- And Active-Control, Parallel Arm, Phase 3 Trial To Evaluate the Efficacy And Safety Of CG5503 ER in Subjects with Moderate To Severe Chronic Low Back Pain**

**Investigation #2: Study R331333-PAI-3015: A Randomized-Withdrawal Phase 3 Study Evaluating the Safety and Efficacy of CG5503 ER in Subjects with Painful Diabetic Peripheral Neuropathy**

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 (Study R331333-PAI-3011) YES  NO

Investigation #2 (Study R331333-PAI-3015) 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:

N/A

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 (Study R331333-PAI-3011) YES  NO

Investigation #2 (Study R331333-PAI-3015) YES  NO

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

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1: **Study R331333-PAI-3011: A Randomized, Double-Blind, Placebo- And Active-Control, Parallel Arm, Phase 3 Trial To Evaluate the Efficacy And Safety Of CG5503 ER in Subjects with Moderate To Severe Chronic Low Back Pain**

Investigation #2: **Study R331333-PAI-3015: A Randomized-Withdrawal Phase 3 Study Evaluating the Safety and Efficacy of CG5503 ER in Subjects with Painful Diabetic Peripheral Neuropathy**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1(Study R331333-PAI-3011)

IND # 61345            YES             ! NO   
! Explain:

Investigation #2(Study R331333-PAI-3015)

IND # 61345            YES             ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

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

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

N/A

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Name of person completing form: **Dominic Chiapperino, Ph.D.**  
Title: **Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products**  
Date: **August 25, 2011**

Name of Office/Division Director signing form: **Bob A. Rappaport, M.D.**  
Title: **Director, Division of Anesthesia, Analgesia, and Addiction Products**

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

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

DOMINIC CHIAPPERINO  
08/25/2011

BOB A RAPPAPORT  
08/25/2011

## STATEMENTS OF CLAIMED EXCLUSIVITY

Pursuant to 21§CFR 314.108(b)(5) Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) is hereby claiming 3 years of exclusivity for NUCYNTA™ ER (tapentadol) extended release oral tablets.

NDA 22-304 (tapentadol immediate release tablets), was submitted under section 505(b) of the act and approved after September 24, 1984. This application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that are essential to approval of the application. Accordingly, the agency shall not make effective for a period of 3 years after the date of approval of this application the approval of a 505(b)(2) application or an abbreviated new drug application for the conditions of approval of this application, or an abbreviated new drug application submitted pursuant to an approved petition under section 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of this application.

**DEBARMENT CERTIFICATION  
TAPENTADOL ER**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.



Robert O'Donnell, PhD  
Vice President  
Regulatory Affairs, Neuroscience

06 November 2009

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 200533 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Nucynta ER Established/Proper Name: tapentadol Dosage Form: extended-release oral tablets		Applicant: Janssen Pharmaceuticals, Inc. (c/o Johnson & Johnson Product Research and Development, LLC) Agent for Applicant (if applicable): N/A
RPM: Dominic Chiapperino, Ph.D., Senior Regulatory Project Manager		Division: Division of Anestheisa, Analgesia, and Addiction Products
<p><u>NDA's:</u> NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2) Efficacy Supplement:    <input 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> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):  N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>August 28, 2011</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>		CR, Oct. 1, 2010

<sup>1</sup> 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.

<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 <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</p>	N/A
❖ Application Characteristics <sup>2</sup>	
<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><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>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>REMS: <input checked="" type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input checked="" type="checkbox"/> ETASU  <input type="checkbox"/> REMS not required</p> <p>Comments:</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)	N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	N/A
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<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

<sup>2</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.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	N/A
<ul style="list-style-type: none"> <li>(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></li> </ul>	N/A
<ul style="list-style-type: none"> <li>(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></li> </ul>	N/A
<ul style="list-style-type: none"> <li>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></li> </ul>	<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"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	N/A
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	N/A
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	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:

N/A

- (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).*

<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>	
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	Finalized, 8/29/11
<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> )	Action(s) and date(s): AP letter, 8/25/11 CR letter, 10/1/10
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Sponsor submitted, 8/23/11
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Sponsor submitted, 12/1/09
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Sponsor submitted, 8/23/11
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Sponsor submitted, 12/1/09
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
❖ 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> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	Sponsor submitted, 8/16/11
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	Review (acceptable), 8/1/11 Letter (acceptable), 3/9/10 Review (acceptable), 3/9/10
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA, 8/1/11 <input checked="" type="checkbox"/> DRISK, 6/23/11, 8/24/10 <input checked="" type="checkbox"/> DDMAC 6/23/11, 9/22/10 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM filing review/Memo of filing meeting, 2/4/10 clinical filing review 1/22/10 nonclinical filing review, 3/11/10 quality/biopharmaceutics filing review, 1/13/10 biometrics filing review, 1/29/10
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included 8/25/11
❖ 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>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>7/6/11</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</li> </ul>	Numerous documents, including acknowledgement letters, Information Request letters and email, other important emails, filing letter, advice letters, Discipline Review letters, etc (organized by reverse chronology)
<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	None
<b>Minutes of Meetings</b>	
<ul style="list-style-type: none"> <li>• Regulatory Briefing (<i>indicate date of mtg</i>)</li> <li>• PeRC</li> </ul>	<input checked="" type="checkbox"/> No mtg  Email (no formal minutes), 8/24/11
<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> </ul>	Post-action meeting, after 1 <sup>st</sup> cycle review, 11/17/10
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	Pre-NDA meeting minutes, 1/21/09; email follow-up advice, 2/12/09
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	EOP2 meeting minutes, 9/22/06
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	Type C clinical program guidance, meeting minutes, 9/30/08; follow-up questions from sponsor, 10/8/08; FDA email response, 10/30/08; Type C clinical program guidance, meeting minutes, 1/13/06; Type C clinical program guidance, meeting minutes, 12/11/03
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)             <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	2 <sup>nd</sup> cycle (Rappaport), 8/25/11 1 <sup>st</sup> cycle (Roca), 10/1/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	2 <sup>nd</sup> cycle (Fields), 8/11/11 1 <sup>st</sup> cycle (Okada), 9/20/10
PMR/PMC Development Templates ( <i>indicate total number</i> )	One PMR(PREA requirement):  PREA PMR template, 8/25/11

<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	See CDTL and Clinical reviews (no separate TL reviews)
<ul style="list-style-type: none"> <li>Clinical reviews (with TL co-signing) (<i>indicate date for each review</i>)</li> </ul>	2 <sup>nd</sup> cycle (Kilgore/Fields), 7/29/11 1 <sup>st</sup> cycle (Brodsky/Okada), 8/19/10
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input 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> )	Addressed on p. 17 of Kilgore/Fields 2 <sup>nd</sup> cycle clinical review, and on p. 18 of Brodsky/Okada 1 <sup>st</sup> cycle clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	CSS consulted DPP, consult review (Alfaro/Khin/Laughren), 8/1/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	C II recommended 2 <sup>nd</sup> cycle memo (Klein), 8/3/11; 2 <sup>nd</sup> cycle review (Lerner/Klein), 7/12/11; 1 <sup>st</sup> cycle review (Lerner/Love/Klein), 9/10/10
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<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>	REMS, submitted 8/23/11; REMS Supporting Document, submitted, 8/23/11; DRISK REMS review (Auth/Karwoski), 8/24/11; Emailed REMS comments (Chiapperino), 8/16/11; Advice letter, 7/19/11; DRISK REMS review (LaCivita/Karwoski), 6/22/11; Letter giving notice of meeting with industry to discuss class REMS, 5/5/11; REMS notification letter (class REMS), 4/18/11; REMS Memo (Won/Hertz), 4/18/11 Consult Request to OSE for REMS review (2 <sup>nd</sup> cycle), 3/10/11; Advice letter (1 <sup>st</sup> cycle) for DRISK REMS comments, 9/21/10; DRISK REMS review (LaCivita/Toyserkani), 8/6/10; REMS notification letter (revisions needed), 4/22/10; REMS Memo (Lapteva), 4/22/10; Consult Request to OSE for REMS review (1 <sup>st</sup> cycle), 12/29/09
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	Clinical Inspection Summary addendum (Leinbenhaut/Purohit-Sheth), 7/14/11; VAI letter, 7/7/11;

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

	NAI letter, 7/7/11; Clinical Inspection Summary (Leinbenhaut/Purohit-Sheth), 9/20/10; Request for DSI clinical inspections, 1/21/10
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None (co-signed primary review)
Statistical Review(s) (indicate date for each review)	2 <sup>nd</sup> cycle review not needed; 1 <sup>st</sup> cycle review (Zhou/Price), 8/27/10
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None (co-signed primary review)
Clinical Pharmacology review(s) (indicate date for each review)	2 <sup>nd</sup> cycle review (Lee/Xu), 7/29/11; 1 <sup>st</sup> cycle review (Lee/Doddapaneni), 8/9/10
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	Inspect. Summary (Dasgupta/Yau), 8/5/11 Memo (b) (4) 5/5/11; DSI Consult, request for biopharmaceutical inspections, 4/28/11
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	2 <sup>nd</sup> cycle review not needed; 1 <sup>st</sup> cycle memo (Wasserman), 8/9/10
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	2 <sup>nd</sup> cycle review not needed; 1 <sup>st</sup> cycle review (Emami/Wasserman), 8/6/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review (Young) for NDA 022304 (immediate release formulation)
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <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 Branch Chief co-signed primary reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	1 <sup>st</sup> cycle review #3 (Bertha/Peri), 5/6/10; 1 <sup>st</sup> cycle review #2 (Bertha/Peri), 3/18/10; 1 <sup>st</sup> cycle review #1 (Bertha/Peri), 1/22/10
❖ Microbiology Reviews <input 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 (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<u>Biopharmaceutics team consulted</u> 2 <sup>nd</sup> cycle review (Suarez/Marroum), 7/21/11; 1 <sup>st</sup> cycle review #3 (Suarez/Marroum), 8/20/10; 1 <sup>st</sup> cycle review #2 (Suarez/Marroum), 7/29/10; 1 <sup>st</sup> cycle review #1 (Suarez/Marroum), 6/14/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	N/A
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	Documented in CMC 1 <sup>st</sup> cycle review (Bertha/Peri), 1/22/10, pp. 94-96 (see above)
❖ 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 sites<sup>6</sup>)</i>	Date completed: 9/15/10 Documented in CMC 1 <sup>st</sup> cycle review #4 (Bertha/Peri), 9/15/10 <input checked="" type="checkbox"/> Acceptable <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>	N/A
❖ 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>6</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.

## 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/  
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DOMINIC CHIAPPERINO  
08/29/2011

## Chiapperino, Dominic

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**From:** Greeley, George  
**Sent:** Wednesday, August 24, 2011 3:04 PM  
**To:** Chiapperino, Dominic  
**Cc:** Addy, Rosemary; Mathis, Lisa; Suggs, Courtney; Rappaport, Bob A; Fields, Ellen  
**Subject:** NDA 200-533 Nucynta ER

**Importance:** High

**Attachments:** 1\_Pediatric\_Record.pdf

Hi Dominic,

The email serves as confirmation of the review for Nucynta ER (tapentadol) conducted by the PeRC PREA Subcommittee on July 6, 2011.

The Division presented a partial waiver for patients birth through seven years of age and a deferral for patients seven to seventeen years of age for the indication of management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The PeRC agreed with the Division to grant a partial waiver for patients ages birth to six years and deferral for patients seven to seventeen years of age for this product.

The amended pediatric record is attached for Nucynta ER.



1\_Pediatric\_Record  
.pdf (69 KB)...

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
10903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

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NDA 200533

**DISCIPLINE REVIEW LETTER**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended release tablets 50, 100, 150, 200, and 250 mg.

We also refer to your submission dated February 28, 2011.

The Office of Surveillance and Epidemiology's Division of Medication Error Prevention and Analysis (DMEPA) has completed its review of the carton and container labeling section of your submission, and has identified the following deficiencies.

DMEPA concludes that the proposed product design, container and blister labels, and carton labeling introduce vulnerability that can lead to medication errors because of similarity to the currently marketed Nucynta (tapentadol) immediate-release tablets. We have the following comments:

General Comments for Container Label and Carton Labeling

1. The font color of the proprietary name chosen for Nucynta ER is similar to the currently marketed Nucynta immediate-release product. The use of the same color contributes to the similarity of these products. This can lead to selection errors and administration of the wrong product because these products may be stored next to each other. This is especially true for the strengths of Nucynta ER and Nucynta that overlap (50 mg and 100 mg).
2. Revise the proprietary name presentation for all UPPERCASE (NUCYNTA ER) to title case (Nucynta ER). This revision aims to improve the relative prominence of the modifier 'ER' and help distinguish Nucynta ER from Nucynta, which appears as NUCYNTA on the container labels and carton labeling.
3. Decrease the prominence of the schedule II symbol.

4. Revise the middle portion of the NDC number in a large font and prominence (xxxx-XXXX-xx) to help differentiate Nucynta ER from Nucynta NDC numbers. Pharmacists use this portion of the NDC number to ensure that the correct product is dispensed.
5. Add the dosing frequency statement, *Twice daily*, to the principal display panel to minimize wrong frequency of administration errors. Additionally, this may improve differentiation from Nucynta (tapentadol) tablets, which is dosed every 4 to 6 hours.
6. Add the statement, *Swallow tablets whole. Do not chew, crush or dissolve*, to the principal display panel.
7. Revise the medication guide statement to read as follows:

Dispense the (b)(4) Medication Guide to each patient

#### Container Label

8. Revise the overall design to differentiate Nucynta ER containers labels from Nucynta. When compared side-by-side, these labels are visually similar. This visual similarity contributes to wrong drug and wrong strength errors. Revise accordingly.
9. Delete the blue rectangular box surrounding the proprietary name. This box appears on the container labels of Nucynta immediate-release tablets and contributes to the visual similarity between both Nucynta ER and Nucynta container labels.
10. Revise the statement: (b)(4) to read Usual Dosage: See package insert for full prescribing information.

#### Carton Labeling

11. Revise the net quantity statement to read as follows:

100 tablets (10 x 10 count blister cards)

#### Hospital Unit-Dose Blister Label

12. Differentiate your product strengths with the use of color, boxing, or some other means, so that the Nucynta ER 50 mg and 100 mg are distinct from Nucynta 50 mg and 100 mg strength tablets. Additionally, the Nucynta ER strengths should be differentiated from one another. Revision of the strength differentiation may reduce the likelihood of wrong drug (Nucynta ER vs. Nucynta) and wrong strength selection errors since unit dose blisters may be stored apart from the cartons.
13. Decrease the prominence of the schedule II symbol.

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 Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PARINDA JANI  
08/02/2011



NDA 200533

**ADVICE/INFORMATION REQUEST**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) dated November 30, 2009, received December 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended-release tablets 50, 100, 150, 200, and 250 mg.

We also refer to your submissions dated February 28, and May 25, 2011.

We are reviewing the proposed Risk Evaluation and Mitigation Strategy (REMS) section of your submission and have the following comments and information requests. Please note that these are interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application. In order to continue our evaluation of your NDA, we request a prompt written response to the following:

**1. REMS Document**

Appendix A contains the necessary revisions to the REMS document in track changes. The following materials are part of the REMS and must be appended to the REMS:

- Medication Guide
- Dear Healthcare Professional Letter
- Prescribing Nucynta ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe Nucynta ER
- Nucynta ER Education Confirmation Form
- Nucynta ER REMS website (screen shots of the web pages)

**2. Dear Healthcare Professional Letter**

Appendix B contains the necessary revisions to the document in track changes.

**3. Healthcare Professionals Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER**

Appendix C contains the necessary revisions to the document in track changes.

**4. Education Confirmation Form**

Appendix D contains the necessary revisions to the form in track changes.

**5. REMS Website**

Make the necessary changes on the landing page of the Nucynta ER REMS website.

*[Second paragraph]*



Regarding the third paragraph, provide the content for “click here.”

*The REMS program is designed to inform patients and healthcare professionals (HCPs) about the risks of NUCYNTA ER. To learn more about the serious risks, including potential for abuse, overdose and addiction, **click here.***

Under step one and the REMS materials - Use the correct name of the training program, Prescribing NUCYNTA<sup>®</sup> ER Healthcare Professional Education Program. Provide a hyperlink in step one to the program.

Include the full indication, including the limitations to the indication, and full boxed warning on the REMS website.

## 6. REMS Supporting Document

- a. All changes in the REMS and Prescribing Information (PI) should also be reflected in the REMS Supporting Document.
- b. In the section titled “Background” remove reference to a reduced risk for abuse with regard to crushing or destroying the extended release property.
- c. Correct the URL for the website for a Nucynta ER REMS.com
- d. Assessments and Surveys
  - o Add an assessment of the mailing of the Dear Healthcare Professional (HCP) Letters to your Information Needed for Assessment: including the number of mailings sent; the targeted specialties that received the Dear HCP Letter, the number of returned mailings, the date of the mailing
  - o The six-month survey should include an implementation survey that identifies timelines and/or milestones identified during the initial six months after the approval of the REMS.
  - o Please also refer to comments previously provided in the advice letter dated Sept 21, 2010, regarding assessments and survey methodology.

## 7. General Comments

- a. REMS materials are not appropriate for use in a promotional manner.
- b. All REMS materials and the REMS Supporting Document should be revised to reflect the content in the final product labeling.
- c. Submit revisions for the proposed REMS with appended materials and the REMS Supporting Document and all other materials in WORD format. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such. The preference is to include as many as possible be in a single WORD document. Please provide a track changes and clean version of all revised materials and documents.

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. Additional revisions may be needed so that the REMS and REMS supporting documents are consistent with the final labeling.

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 Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

Appendix A - REMS Document

Appendix B - Dear Healthcare Provider Letter

Appendix C - Prescribing NUCYNTA<sup>®</sup> ER Healthcare Professional Education Program

Appendix D - NUCYNTA<sup>®</sup> ER Education Confirmation Form

31 Page(s) of Draft REMS has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/  
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PARINDA JANI  
07/19/2011

**Patwardhan, Swati**

**From:** Patwardhan, Swati  
**Sent:** Wednesday, July 13, 2011 12:55 PM  
**To:** 'Dusek, Kathleen [JRDUS]'  
**Subject:** RE: NDA 200533 Information request

Hi Katie,

We are reviewing CMC aspect of NDA 200533 and request following:

The following dissolution acceptance criteria is recommended for Tapentadol Extended Release tablets, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Tapentadol	ER Tablet	II (paddle) (b) (4)	100	pH 6.8 phosphate Buffer, Simulated intestinal fluid (without enzyme)	900,  37 °C ± 0.5 °C	30 minutes: (b) (4) . 180 minutes (b) (4) . 360 minutes (b) (4) % 600 minutes: Not less than (b) (4)

Please revise the specification at 30 minutes accordingly and submit the updated sheet of specifications reflecting this recommendation no later than July 18, 2011.

Thank you

Swati Patwardhan  
Regulatory Health Project Manager for Quality  
Office of New Drug Quality Assessment (ONDQA)  
Center of New Drug Evaluation and Research  
Phone: 301-796-4085  
Fax: 301-796-9748

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/s/  
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SWATI A PATWARDHAN  
07/13/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): DPP, Paul David

FROM (Name, Office/Division, and Phone Number of Requestor): Sandra Saltz, Project Manager, CSS, 301-796-3117

DATE  
6/2/2011

IND NO.

NDA NO.  
200533

TYPE OF DOCUMENT

DATE OF DOCUMENT  
6/2/2011

NAME OF DRUG  
Tapentadol

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
7/2/2011

NAME OF FIRM:

## 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 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: CSS would like to obtain more information on following issues:

1. Is there any evidence that opioid medications contribute to or increase the risk of suicidality? If so, where could we search for the scientific evidence?
2. For the drugs which have a mixed mechanism of action, such as tapentadol, which includes mu-agonist activity with selective norepinephrine and serotonin uptake inhibition (SNRI/SSRI) is there any way to distinguish the cases of suicidality related to SNRI/SSRI activity from the suicidality triggered by the underlying disorders of patients with cancer and other painful terminal diseases.

SIGNATURE OF REQUESTOR  
Sandra L. Saltz

METHOD OF DELIVERY (Check one)  
 DFS  EMAIL  MAIL  HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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SANDRA L SALTZ  
06/03/2011

**MEMORANDUM**

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

**DATE:** May 18, 2011

**TO:** File, NDA 200533

**THROUGH :** n/a

**FROM:** Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**SUBJECT:** Archival of emailed “NDA 200533 (Tapentadol ER), Pediatric Plan”

**APPLICATION/DRUG:** NDA 200533/Nucynta ER (tapentadol) extended-release tablets

The attached email to the sponsor of NDA 200533 was sent May 18, 2011, at the request of DAAAP Medical Team Leader, Ellen Fields, M.D.

**Chiapperino, Dominic**

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**From:** Chiapperino, Dominic  
**Sent:** Wednesday, May 18, 2011 11:43 AM  
**To:** Dusek, Kathleen [PRDUS]  
**Subject:** RE: NDA 200533 (Tapentadol ER), Pediatric Plan

Hi Katie,

The Division has reviewed the revised Pediatric Plan submitted by J&J on April 28, 2011, for NDA 200533, Nucynta ER.

Thus far, we have the following comments:

You are proposing a [REDACTED] (b) (4) study to evaluate the efficacy and safety of multiple doses of tapentadol ER in subjects [REDACTED] (b) (4) experiencing moderate to severe chronic pain. [REDACTED] (b) (4)

[REDACTED] (b) (4)

Please contact me if you have questions at this time.

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  
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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**From:** Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@its.jnj.com]  
**Sent:** Thursday, April 28, 2011 1:15 PM  
**To:** Chiapperino, Dominic

**Subject:** NDA 200533 (Tapentadol ER): Response to FDA request for Revised Pediatric Plan

Dear Dominic:

The revised pediatric plan for NDA 200533 has been submitted to the Agency today. A copy of the cover letter is attached for your information.

**Michael H. Kaufman**

Director, Regulatory Affairs

Johnson & Johnson

Pharmaceutical Research & Development, L.L.C.

Tel: (908) 704-4756

Fax: (908) 722-5113

Email: [mkaufman@its.jnj.com](mailto:mkaufman@its.jnj.com)

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/s/  
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DOMINIC CHIAPPERINO  
05/18/2011



Department of Health and Human Services

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Food and Drug Administration  
10903 New Hampshire Ave  
Building 51  
Silver Spring, MD 20993

Via Electronic Mail

May 6, 2011

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, L.L.C.  
920 US Highway 202  
Raritan, NJ 08869

Attention: Mary Mulligan  
Manager, Global Regulatory Affairs

Dear Ms. Mulligan:

As stated in our letter of April 19, 2011, FDA has determined that a REMS is necessary for long-acting (LA) and extended-release (ER) opioid medications to ensure the benefits of the drugs continue to outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death that result from inappropriate prescribing, misuse, and abuse of these products. Within 120 days from the issuance of the letter, you are required to submit a proposed REMS containing the elements described in the letter.

To provide an opportunity to discuss any questions or concerns with us well in advance of the REMS submission due date, you are invited to a meeting that will be held from 10:00 AM to 12:00 Noon on May 16, 2011. This meeting will only be open to sponsors with approved or pending applications for an LA or ER opioid. The meeting will be held in Room 9201 at the Kirkland Center of the National Labor College, located at 10000 New Hampshire Avenue, Silver Spring, MD 20903. The Kirkland Center has abundant free parking. Information about the Kirkland Center, including directions, can be found at <http://www.acc-kirklandconferencecenter.com/index.cfm>.

Because space is limited, each sponsor is limited to sending three representatives to attend the meeting in person. We will set up an operator assisted teleconference so that additional members of your staff will be able to listen to, but not speak at, the meeting.

Please send the names and titles of the staff who will represent you at the May 16 meeting to Michie Hunt at [michie.hunt@fda.hhs.gov](mailto:michie.hunt@fda.hhs.gov) by close of business Monday, May 9. We require a list of attendees because we will be checking arrivals against a list of names at the door. There will be no exceptions to the rule limiting each company to three representatives at the meeting. You must also provide the names of those who will be participating in the meeting by phone so we can notify the operator of those authorized to participate. Please provide Ms. Hunt with the

names and email addresses of the staff whom you wish to participate in the call by close of business Monday, May 9. She will then place their names on the screening list, which the operator will check before allowing entry into the call. She will also send your staff members the call-in number and passcode.

We encourage you to submit written questions to us in advance of the meeting so that we will be able to consider the questions and be prepared to respond at the meeting. You may address your written questions to Ms. Hunt. In order to give us time to consider your questions in advance of the meeting they should be submitted to Ms. Hunt by close of business Tuesday, May 10.

If you have any additional questions about the meeting, please address them to Ms. Hunt by email or at 301-796-3504.

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SHARON H HERTZ on behalf of BOB A RAPPAPORT  
05/06/2011  
signing for Bob Rappaport, M.D.



NDA 200533

**PRE-APPROVAL REMS NOTIFICATION**

Ortho-McNeil-Janssen Pharmaceuticasl, Inc.  
c/o Johnson & Johnson Pharmaceutical Research and Development, L.L.C.  
1125 Trenton-Harbourton Road  
PO Box 200  
Titusville, NJ 08560

Attention: Michael H. Kaufman  
Director, Regulatory Affairs

Dear Mr. Kaufman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nucynta ER (tapentadol) Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg.

We also refer to the stakeholder, industry, and public meetings, and Advisory Committee meeting held on February 10, March 3, May 4 and 5, May 27 and 28, 2009, and July 22 and 23, 2010, respectively, at which discussions took place concerning a risk evaluation and mitigation strategy (REMS) for the class of long-acting and extended-release opioid products. FDA has analyzed the advice and comments provided during these meetings and has determined the necessary elements of the class-wide REMS.

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for certain long-acting and extended-release opioid products, including Nucynta ER, to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The elements of the REMS are described below.

In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class.

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Nucynta ER would pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Nucynta ER. FDA has determined that Nucynta ER is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Nucynta ER. FDA has also determined that Nucynta ER is a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all extended-release and long-acting opioids, as well as product specific information that is necessary for safe and effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Nucynta ER.

**Elements to Assure Safe Use:** We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a Communication Plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including, at a minimum, the following:

1. The sponsor must ensure that training is provided to prescribers who prescribe Nucynta ER. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to Nucynta ER and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.
3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 6 months, 12 months, and annually after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of your REMS and whether the goals or elements should be modified. Your assessment plan should include the following elements along with the methodology for each element:

1. an assessment of how many prescribers of long-acting and extended-release opioids have successfully completed the training. The assessment should specify performance goals for how many prescribers can be expected to be trained within a certain period, e.g., 50% of prescribers trained within 6 months; 70% within twelve months. We recommend that you consult with accredited CME providers to determine what can be realistically be achieved through an aggressive education program and propose goals accordingly.
2. an independent audit of the quality of the content of the educational materials used by the CME providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS as well as against the Accreditation Council for Continuing Medication Education (ACCME) standards for CME.
3. an evaluation of healthcare providers' awareness and understanding of the serious risks associated with these products (for example, through surveys of healthcare providers) and specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
4. an evaluation of patients' understanding of the serious risks of these products.
5. a surveillance plan that includes monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics. Surveillance needs to include information on changes in abuse, misuse, overdose addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
6. an evaluation of drug utilization patterns. Include methodology for monitoring patterns of prescribing to identify changes in access to these products.
7. an evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills. Provide the methodology for this analysis.

FDA strongly recommends that sponsors make provision in the single shared system for joint assessments of the effectiveness of the REMS.

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS. Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a model for the proposed REMS (see Appendix C).

Additionally, all relevant proposed REMS materials, including educational materials, should be appended to the proposed REMS. FDA expects that the content of the educational materials will

follow the attached outline, and contain more specific content on the proposed topics than is contained in the outline. FDA will review and approve the content of the training. However, FDA understands that CME providers will take the approved content and develop specific materials for training (e.g., slides, internet-based training). Accordingly, FDA does not expect the sponsor to provide and attach to the REMS the specific materials that will be used to train prescribers.

Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include the approved documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining how the REMS will be implemented. The same supporting document may be submitted by each member of the single, shared system.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

For administrative purposes, designate the proposed REMS submission “**PROPOSED REMS for NDA 200533/S-####**” and all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA 200533.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

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

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:  
REMS Appendices A, B, and C

## **APPENDIX A: CONTENT OF EDUCATION PROGRAM**

The training for prescribers required by the elements to assure safe use must contain the following content:

1. General information for safe opioid prescribing
  - a. Patient selection and assessment
    - i. Determine goal of therapy
    - ii. Assessment of the risk of abuse, including history of substance abuse and serious mental illness
    - iii. When relevant, determining if patient is opioid tolerant
  - b. Considerations when prescribing opioids
    - i. Pharmacokinetics and potential for overdose
    - ii. Addiction, abuse, and misuse
    - iii. Intentional abuse by patient or household contacts
    - iv. Interactions with other medications/substances
  - c. Managing patients taking opioids
    - i. Establishing goals for treatment and evaluating pain control
    - ii. Use of Patient Provider Agreements (PPAs)
    - iii. Adherence to a treatment plan
    - iv. Recognizing aberrant behavior
    - v. Managing adverse events
  - d. Initiating and modifying dosing of opioids for chronic pain
    - i. As first opioid
    - ii. Converting from one opioid to another
      1. Converting from immediate-release to extended-release and long-acting products
      2. Converting from one extended-release and long-acting product to another
    - iii. Titrating to effect/tolerability
    - iv. How to deal with missed doses
  - e. Maintenance
    - i. Reassessment over time
    - ii. Tolerance
  - f. Monitoring patients for misuse and abuse

- i. Utilization of prescription monitoring programs to identify potential abuse
    - ii. Understanding the role of drug testing
    - iii. Screening and referral for substance abuse treatment
  - g. How to discontinue opioid therapy when it is not needed any longer
- 2. Product Specific Information
  - a. Pharmacokinetic characteristics
  - b. Product specific toxicity
  - c. Requirements for opioid tolerance for certain long-acting and extended-release products
  - d. Individual product information modules
    - i. Fentanyl transdermal system
    - ii. Hydromorphone ER
    - iii. Methadone (For the treatment of moderate to severe pain not responsive to non-narcotic analgesics)
    - iv. Morphine ER
    - v. Oxycodone ER
    - vi. Oxymorphone ER
    - vii. Buprenorphine (for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time)
    - viii. New products
- 3. Patient counseling
  - a. Information about prescribed opioid
  - b. How to take opioid properly
    - i. Adherence to dosing regimen
    - ii. Risk from breaking, chewing, crushing certain products
  - c. Reporting adverse effects
  - d. Concomitant use of other CNS depressants, alcohol, or illegal drugs
  - e. Discontinuation of opioid
  - f. Risks associated with sharing, i.e., overdose prevention
  - g. Proper storage in the household
    - i. Avoiding accidental exposure

- h. Avoiding unsafe exposure by preventing theft and proper disposal
- i. Purpose and content of Patient Provider Agreement

## **APPENDIX B: PATIENT EDUCATION**

Materials to provide to patients as part of patient counseling must include:

1. How to take opioid properly
  - a. Adherence to dosing regimen
  - b. Risk from breaking, chewing, crushing certain products
  - c. Symptoms of overdose
2. Reporting adverse effects
3. Concomitant use of other CNS depressants, alcohol, or illegal drugs
4. Discontinuation of opioid
5. Risks associated with sharing
6. Proper storage in the household
  - a. Avoiding accidental exposure
7. Avoiding unsafe exposure by preventing theft and proper disposal
8. Purpose and content of Patient Treatment Agreement
9. Links to Web sites with more information about topics 1 through 8

**APPENDIX C: REMS TEMPLATE**

**Initial REMS Approval: XX/XXXX**

**Most Recent Modification: XX/XXXX**

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL:**

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release (ER) and long-acting (LA) opioids while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

**II. REMS ELEMENTS:**

**A. Medication Guide or PPI**

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

**B. Communication Plan**

A communication plan is not required.

**C. Elements To Assure Safe Use**

1. The sponsor must ensure that training is provided to prescribers who prescribe DRUG. An outline of the content for this information is described in Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To assure access to DRUG and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.
2. The sponsor must provide to prescribers information that the prescriber can use to educate patients in the safe use, storage, and disposal of opioids. An outline of the content for this information is described in Appendix B.
3. The sponsor must inform prescribers of the existence of the REMS and the need to successfully complete the necessary training.

#### **D. Implementation Plan**

An implementation plan is not required.

#### **E. Timetable for Submission of Assessments**

COMPANY will submit REMS Assessments to the FDA no less frequent than 6 months, 12 months, and annually after the REMS is initially approved from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/  
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SHARON H HERTZ on behalf of BOB A RAPPAPORT  
04/18/2011  
Signing for Bob Rappaport, M.D.

**MEMORANDUM**

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

**DATE:** April 1, 2011

**TO:** File, NDA 200533

**THROUGH :** n/a

**FROM:** Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**SUBJECT:** Archival of emailed "Information Request – Revise pediatric plan"

**APPLICATION/DRUG:** NDA 200533/Nucynta ER (tapentadol) extended-release tablets

The attached email to the sponsor of NDA 200533 was sent April 1, 2011, at the request of DAAAP Medical Team Leader, Ellen Fields, M.D.

## Chiapperino, Dominic

---

**From:** Chiapperino, Dominic  
**Sent:** Friday, April 01, 2011 12:25 PM  
**To:** 'Kaufman, Michael [PRDUS]'  
**Subject:** Information Request - Revised pediatric plan

Hi Michael,

Referring to NDA 200533 for Nucynta ER, we have the following request.

We acknowledge your submission of a pediatric plan with NDA 200533, that includes deferred studies of pharmacokinetics, safety, and efficacy in pediatric patients [REDACTED] (b) (4)

The Division has determined that the population of pediatric patients with chronic pain less than 7 years of age is too small to study, making studies highly impractical. Therefore, we request that you submit a revised pediatric plan requesting a waiver for studies in patients less than 7 years, with supportive information regarding the small number of patients in this age group with chronic pain. We also request a revision of the deferral request to include PK, safety, and efficacy studies in pediatric patients ages 7 to 17. The plan must include a timeline that states the date of final protocol submission to the Agency, date of study start, and date of final report submission to the Agency.

Thank you, and please contact me if you have any questions.

Best regards,  
Dominic

Dominic Chiapperino, Ph.D.  
*Senior Regulatory Health Project Manager*  
*FDA, Center for Drug Evaluation and Research*  
*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/  
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DOMINIC CHIAPPERINO  
04/01/2011



NDA 200533

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Michael H. Kaufman  
Director, Regulatory Affairs

Dear Mr. Kaufman:

We acknowledge receipt on February 28, 2011, of your resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended-release tablets, 50, 100, 150, 200, and 250 mg.

We consider this a complete, class 2 response to our October 1, 2010, action letter. Therefore, the user fee goal date is August 28, 2011.

If you have any questions, call me at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Dominic Chiapperino, Ph.D.  
Senior Regulatory Health Project Manager  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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DOMINIC CHIAPPERINO  
03/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Office of Surveillance and Epidemiology ATTN: Danyal Chaudhry, OSE SRPM</b>		FROM: <b>Division of Anesthesia and Analgesia Products -- Dr. Bob Rappaport, M.D. Point-of-contact: Dominic Chiapperino, Ph.D. Senior Regulatory Project Manager, 301-796-1183</b>		
DATE <b>Mar. 10, 2011</b>	IND NO.	NDA NO. <b>200533</b>	TYPE OF DOCUMENT <b>NDA Resubmission</b>	DATE OF DOCUMENT <b>Recvd. Feb. 28, 2011</b>
NAME OF DRUG <b>Nucynta ER (tapentadol) extended release tablets</b>		PRIORITY CONSIDERATION <b>Resubmission Class 2</b>	CLASSIFICATION OF DRUG <b>Type 3</b>	DESIRED COMPLETION DATE <b>July 10, 2011 (some parts sooner, e.g., labeling comments)</b>
NAME OF FIRM: <b>Johnson &amp; Johnson on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.</b>				
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 checked="" type="checkbox"/> RESUBMISSION <input 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 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		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please review various sections of this resubmitted NDA (#200533, with PDUFA date, Aug. 28, 2011) from a drug safety and risk management perspective. It has the following components for OSE review: <ul style="list-style-type: none"> <li>• Package Insert labeling</li> <li>• Medication Guide labeling</li> <li>• Carton and Container labeling</li> <li>• Proposed REMS as part of risk management plan</li> <li>• Updated proprietary name review (sponsor should also send request)</li> </ul>				
This drug product is an opioid schedule II compound (tapentadol) in an extended release formulation. An immediate release formulation is already approved and marketed (NDA 22-304). NDA 200533 is fully electronic (eCTD format) and all files can be found at: <a href="\\CDSESUB1\EVSPROD\NDA200533\200533.ENX">\\CDSESUB1\EVSPROD\NDA200533\200533.ENX</a> Some relevant files are also saved at: <a href="\\dfs01\ode2\DAAP\NDA and sNDA\NDA 200533 (NucyntaER-tapentadol J&amp;J)&gt;">\\dfs01\ode2\DAAP\NDA and sNDA\NDA 200533 (NucyntaER-tapentadol J&amp;J)&gt;</a>				

This network folder will also be used for shared files/editing. All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Project Manager.	
SIGNATURE OF REQUESTER <b>Dominic Chiapperino (signed electronically)</b>	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/  
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DOMINIC CHIAPPERINO  
03/10/2011

## REQUEST FOR CONSULTATION

TO (Office/Division):

Controlled Substance Staff (CSS, HFD-009)  
ATTN: Sandy Saltz, Corinne Moody

FROM (Name, Office/Division, and Phone Number of Requestor):

Division of Anesthesia, Analgesia, and Rheumatology  
Products -- Dr. Bob Rappaport, M.D.  
point-of-contact:  
Dominic Chiapperino, Ph.D., Senior Regulatory Project  
Manager, 301-796-1183

DATE  
March 10, 2011

IND NO.

NDA NO.  
200533

TYPE OF DOCUMENT  
Resubmission, Class 2

DATE OF DOCUMENT  
Feb. 28, 2011

NAME OF DRUG  
Nucynta ER (tapentadol)  
extended release tablets

PRIORITY CONSIDERATION  
No

CLASSIFICATION OF DRUG  
3

DESIRED COMPLETION DATE  
July 10, 2011

NAME OF FIRM: Ortho- McNeil-Janssen Pharmaceuticals, Inc. (J & J)

### 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 checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input 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:**

Please review the resubmission of NDA 200533 (tapentadol is an opioid Schedule II, this is an extended release formulation) from an abuse liability perspective, including considerations for labeling and post-market studies, and agreements.

This is an eCTD application, and all NDA submissions/files can be accessed via the EDR/GSReview. The PDUFA date is August 28, 2011, and we want to be prepared to take our action as early as possible in August.

Reference ID: 2916354

SIGNATURE OF REQUESTOR Dominic Chiapperino (electronically signed)	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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DOMINIC CHIAPPERINO  
03/10/2011

**Chiapperino, Dominic**

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**From:** Chiapperino, Dominic  
**Sent:** Thursday, December 09, 2010 3:46 PM  
**To:** 'Kaufman, Michael [PRDUS]'  
**Subject:** RE: NDA 200533 (tapentadol ER): General Correspondence - Request for clarification on FDA minutes to Complete Response meeting

Dear Michael,

The Division has reviewed your request for clarification in your December 7, 2010, submission.

Specifically, J & J requested comment as follows, excerpted from the submission's cover letter:

At this time, we wish to clarify a statement noted in the FDA minutes, specifically, in the Clinical and Statistical Question 4 discussion under the third paragraph. In this paragraph it states that "J&J will need to demonstrate the safety, particularly with respect to any difficulty in swallowing, of the TRF tablets." We propose to demonstrate the safety of the TRF tablet formulation by providing safety data including review of any potential adverse event reports suggestive of difficulty swallowing, from the clinical studies that used the TRF tablets. We respectfully request confirmation that our approach to review the available safety data from the clinical program with the TRF dosage form is sufficient to demonstrate the safety of the TRF tablets with respect to difficulty to swallowing the tablet and potential choking hazard.

The Division has the following comments:

Your proposal to review the available safety data from the clinical program with the TRF dosage form to demonstrate the safety of the TRF tablets with respect to difficulty swallowing and becoming a potential choking hazard will yield an important part of the information needed; however, it is unlikely to be sufficient to address the concern. The reason is that the adverse events that have been reported with a drug with a similar formulation as yours have arisen in the post-marketing period; there may have been factors in the controlled setting of a clinical trial that were no longer present once the product became widely available, resulting in the safety signal. The goal will be to evaluate for these potential factors and provide data that will inform for appropriate labeling for oral administration. This may require additional in vitro assessments and, potentially, evaluation in a clinical trial.

Please contact me if J & J had need of further discussion on this point.

Thank you and best regards,  
Dominic

Dominic Chiapperino, Ph.D.  
*Senior Regulatory Health Project Manager*  
*FDA, Center for Drug Evaluation and Research*  
*Division of Anesthesia and Analgesia Products*  
*10903 New Hampshire Avenue*

Reference ID: 2875394

12/9/2010

*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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**From:** Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@its.jnj.com]  
**Sent:** Tuesday, December 07, 2010 2:11 PM  
**To:** Chiapperino, Dominic  
**Subject:** NDA 200533 (tapentadol ER): General Correspondence - Request for clarification on FDA minutes to Complete Response meeting

Dear Dominic:

The following correspondence has been official submitted to NDA 200533 (tapentadol ER). I am sending you a copy of the letter for your information. We look forward to receiving a response from the Division shortly.

Thank you.

**Michael H. Kaufman**  
Director, Regulatory Affairs  
**Johnson & Johnson**  
**Pharmaceutical Research & Development, L.L.C.**  
Tel: (908) 704-4756  
Fax: (908) 722-5113  
Email: [mkaufman@its.jnj.com](mailto:mkaufman@its.jnj.com)

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/s/  
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DOMINIC CHIAPPERINO  
12/09/2010



NDA 200533

**MEETING MINUTES**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) Extended-Release Tablets 50, 100, 150, 200, and 250 mg.

We also refer to the teleconference between representatives of Johnson and Johnson (J & J) and the FDA on November 9, 2010. The purpose of the teleconference was to clarify the required elements of a Complete Response submission for a new review cycle of NDA 200533.

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

If you have any questions, call me at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Dominic Chiapperino, Ph.D.  
Senior Regulatory Health Project Manager  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Memorandum of meeting minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** Post-Action  
**Teleconference Date and Time:** November 9, 2010, 9:30 to 10:30 AM  
**Application Number:** NDA 200533  
**Product Name:** Nucynta ER (tapentadol) Extended Release Tablets  
**Indication:** The management of moderate to severe chronic pain in patients 18 years of age or older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.  
**Sponsor/Applicant Name:** Johnson and Johnson Pharmaceutical Research and Development, L.L.C.  
**Meeting Chair:** Rigoberto Roca, M.D., Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)  
**Meeting Recorder:** Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAP

**Attendees:**

<b>FDA Participants</b>	<b>Title</b>
Bob A. Rappaport, M.D.	Director, Division of Anesthesia and Analgesia Products (DAAP)
Rigoberto Roca, M.D.	Deputy Director, DAAP
Ellen Fields, M.D.	Clinical Team Leader, DAAP
Armaghan Emami, Ph.D.	Pharmacology Toxicology Reviewer, DAAP
Dominic Chiapperino, Ph.D.	Senior Regulatory Health Project Manager, DAAP
David J. Lee, Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP2)
Craig Bertha, Ph.D.	CMC Reviewer, Office of New Drug Quality Assessment (ONDQA)
Sandra Suarez Sharp, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Susan Leibenhaut, M.D.	Medical Officer, Office of Compliance, Division of Scientific Investigations
<b>J &amp; J Participants</b>	<b>Title</b>
James Buckley	Associate Director, Global Regulatory Affairs, CMC
Linda Carter	Senior Director, Global Regulatory Affairs, FDA Liaison Office
Mila Etropolski, M.D.	Senior Director, Clinical Leader
Donald Heald, Ph.D.	Vice President, Clinical Pharmacology Therapeutic Area Head - Neuroscience
Michael Kaufman, R.Ph.	Director, Global Regulatory Affairs

Rebecca Martinez, M.S.	Manager, Regulatory Affairs
Akiko Okamoto, Sc.D.	Director, Clinical Biostatistics
Camille Orman, Ph.D.	Director, Clinical Biostatistics
Christine Rauschkolb, M.D., Ph.D.	Vice President, Compound Development Team Leader
Yinka Williams, Ph.D.	Senior Director, Pharmaceutical Development & Manufacturing Sciences
Peter Zannikos, Ph.D.	Director, Clinical Pharmacology
Marielle Eerdeken	Vice President, Head of Late Stage Clinical Development, Grünenthal GmbH
Thomas Huijbers	Associate Director, Global Regulatory Affairs, Grünenthal GmbH

**Background:**

J & J's original NDA for Nucynta ER (tapentadol) Extended-Release Tablets, NDA 200533, received a Complete Response from DAAP in a letter dated October 1, 2010. J & J is seeking feedback from FDA on the elements they propose to include in a resubmission of their NDA for a second review cycle. Preliminary comments were provided to J & J in a November 8, 2010, communication that included DAAP's responses to questions from the October 18, 2010, briefing package submitted by J & J. After reviewing the responses, J & J requested that the meeting be converted to a teleconference, as they only wished to obtain clarification on two points, as described in J & J's email communication dated November 8, 2010.

**Meeting Discussion:**

Below are the questions from J & J's October 18, 2010, briefing package and FDA's responses, as sent in the November 8, 2010, Preliminary Comments letter. The questions are in italicized font and FDA's responses are in bolded font. J & J's written requests for clarification from their November 8, 2010, email communication are inserted as italicized and bolded text. Discussion during the teleconference is summarized in normal font.

*CHEMISTRY, MANUFACTURING, AND CONTROLS*

*Question 1. Does the Agency agree with our revised dissolution specifications? If it is not possible to provide an assessment of the specifications at this time, does the Agency agree with the approach we have taken in setting the specifications?*

**FDA Response:**

**We agree in general with the time points you have selected. In addition, the proposed specifications seem appropriate; however, their acceptability will be decided upon review of the submission of the complete response.**

Discussion:

No further discussion of this question was necessary.

*BIOPHARMACEUTICAL DEVELOPMENT AND CLINICAL PHARMACOLOGY*

*Question 2. Does the Agency agree that bioequivalence has been established for the 4 dosage strengths of the therapeutic dose range for tapentadol ER (TRF), i.e., 100, 150, 200, and 250 mg?*

**FDA Response:**

**Based on the information presented in the meeting package, it appears that bioequivalence (BE) has been established for the 4 strengths (i.e., 100, 150, 200, and 250 mg) of the tapentadol ER tablet. However, the acceptance of the study results will be a review issue.**

Discussion:

No further discussion of this question was necessary.

*Question 3. Does the Agency agree that a biowaiver request for the tapentadol ER intermediate strengths (100, 150, and 200 mg), that would include in vitro comparative dissolution profile data and f2 calculations, is not needed as bioequivalence studies have been conducted with the intermediate strengths and the study reports for these bioequivalence studies will be included in our response to the Complete Response Letter?*

**FDA Response:**

**Yes, we agree that a biowaiver request with supporting information for Tapentadol ER intermediate strengths (i.e., the 100, 150, and 200 mg) is not required provided that the Agency finds acceptable the in vivo BE studies conducted with these strengths in support of the bridging between the to-be-marketed formulation and the pilot/registration formulation.**

Discussion:

No further discussion of this question was necessary.

*CLINICAL AND STATISTICAL*

*Question 4. Does the Agency agree that approval for the tapentadol to-be-marketed 50-mg TRF tablet could be granted based on the results of Study PAI-1059/HP82 and the following rationale: (i) the 50-mg dose is intended to be used only during initial titration, (ii) serum tapentadol concentrations achieved with the 50-mg titration dose do not exceed the concentrations achieved with therapeutic doses (100 to 250 mg) of the tapentadol to-be-marketed TRF formulation, (iii) comparable safety profiles have been documented with the 50-mg to-be-marketed TRF and PR2 Phase 3 study formulations, (iv) a cross-study comparison demonstrated that the tapentadol to-be-marketed TRF formulation exhibits linear and predictable pharmacokinetics across the entire dose range (50 to 250 mg)?*

**FDA Response:**

**The results presented in the meeting package indicate that to-be-marketed 50 mg TRF tablet is NOT bioequivalent (C<sub>max</sub> 90% CI: 123 – 135) to Phase 3 PR2 formulation.**

**However, the 50 mg tablet could potentially be approved after review of the rationale proposed above, including the data supporting the safety profile and the pharmacokinetics of the TRF formulation.**

***Sponsor's Request for Clarification:***

***We would like to clarify that in support of the rationale provided in Sponsor's Question #4, item (iii) (above), the complete response will contain clean data for the first three weeks (the open-label titration) from all patients enrolled in the Phase 3 DPN study (PAI-3027) conducted with tapentadol ER TRF. The analyses that will be provided will be the same as those submitted for the subset of the enrolled patients that were included in the briefing book. Study enrollment completed on 03 November 2010. Does the Agency agree with this proposal?***

**Discussion:**

The Division stated that the proposal is acceptable. However, the Division identified two concerns that would need to be addressed within the Complete Response NDA submission.

First, there is the issue of "switchability," or interchangeability, of the tablets of different strengths to achieve a particular total dose. For example, a patient might utilize four 50 mg TRF tablets during the titration phase to reach an intended dose of 200 mg, and then switch to the 200 mg TRF tablet once the titrated dose is reached. Conversely, if a patient happens to run out of their higher strength tablets, they may choose to take multiple 50 mg TRF tablets that they may have left over from their titration period. It is not clear, in light of the lack of bioequivalence between the 50 mg TRF tablet and the 50 mg PR2 tablet, whether clinical scenarios such as these would result in unexpected consequences. J & J was requested to evaluate their options and submit their plan on how to address this in the Complete Response submission.

Second, the Division requested that J & J evaluate whether the formulation of the TRF tablet causes the tablet to become sticky or expanded upon getting moist, making it difficult to swallow and a potential choking hazard. J & J will need to demonstrate the safety, particularly with respect to any difficulty in swallowing, of the TRF tablets.

J & J acknowledged these concerns and agreed that they would address both in their Complete Response submission.

***Question 5. Does the Agency agree with the contents of the proposed Complete Response Safety Update of NDA 200533?***

**FDA Response:**

**The contents of the proposed Complete Response Safety Update are acceptable.**

**Discussion:**

No further discussion of this question was necessary.

*Question 6. Does the Agency concur that the final Clinical Study Reports for Studies PAI-3014/KF16 and PAI-3020/KF41 described in the 4-Month Safety Update do not need to be submitted with the Complete Response Safety Update?*

**FDA Response:**

**Since the final clinical study reports for Studies PAI-3014/KF16 and PAI-3020/KF41 were submitted to IND 61,345, you do not need to resubmit them with the Complete Response Safety Update.**

Discussion:

No further discussion of this question was necessary.

*Question 7. Does the Agency agree with the Sponsor's plan to present ongoing clinical study data in a manner similar to that previously presented in the Integrated Summary of Safety of NDA 200533 and the 4-MSU?*

**FDA Response:**

**Yes, your plan is acceptable.**

Discussion:

No further discussion of this question was necessary.

*Question 8. For the tapentadol ER Complete Response Safety Update, are the proposals for the submission of post-marketing experience on tapentadol drug safety acceptable to the Agency?*

**FDA Response:**

**Yes, your proposal is acceptable.**

Discussion:

No further discussion of this question was necessary.

*Question 9. The Sponsor proposes to provide patient profiles and the analysis dataset for the completed Phase 3 Study PAI-3010/KF18 only. Does the Agency agree that this is acceptable?*

**FDA Response:**

**Yes, your proposal is acceptable.**

Discussion:

No further discussion of this question was necessary.

*Question 10. For all completed studies, the Sponsor will provide case report forms (CRFs) and narratives for all subjects who died, had a serious adverse event, or discontinued study*

*medication due to an adverse event as outlined in the briefing document. Does the Agency agree with this approach?*

**FDA Response:**  
**Yes, this approach is acceptable.**

Discussion:  
No further discussion of this question was necessary.

*REGULATORY*

*Question 11. Does the Agency agree with the proposed content of the submission that will be provided in response to the 01 October 2010 Complete Response Letter?*

**FDA Response:**  
**Yes, the proposed content is acceptable. Additionally, Module 2 should contain Summaries of Clinical Pharmacology and Biopharmaceutics, including formulation information used in bioequivalence studies.**

*Sponsor's Request for Clarification:*

*We will submit a revised Module 2.7.1 (including formulation information used in the bioequivalence studies), the full study reports for the 5 completed bioequivalence studies (PAI-1057, PAI-1058, PAI-1059, PAI-1060, and PAI-1061), and the corresponding tapentadol concentration-time data as SAS transport files. Does the Agency agree with this proposal?*

Discussion:  
FDA clarified that its initial response [above] was intended to elicit from J & J, as part of their Complete Response submission, a document in Module 2 that summarized the collective results of these five clinical studies. J & J's proposal is acceptable, provided that, in addition to their proposed elements, they also include the desired substantive summary of results from the five clinical studies.

*Question 12. Will the scheduling of the Advisory Committee meeting for the tapentadol ER tablet (to-be-marketed TRF formulation) be contingent upon the date of the Complete Response re-submission?*

(b) (4)

**FDA Response:**  
**We are reconsidering the need for this Advisory Committee meeting and will make a final decision upon our review of your complete response.**

Discussion:  
No further discussion of this question was necessary.

Teleconference outcomes and final understandings:

1. J & J agreed that they would give consideration to the switchability concern related to the 50 mg TRF tablet, and address this concern in their Complete Response submission.
2. J & J acknowledged the concern related to the ability of patients to safely and easily swallow TRF tablets, and stated that they would investigate and address the issue in their Complete Response submission.
3. J & J stated that they would provide the desired summary of bioequivalence clinical study results in Module 2, which would make their proposed content for Module 2 of their Complete Response acceptable to FDA.

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/s/  
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DOMINIC CHIAPPERINO  
11/17/2010



NDA 200533

**PRELIMINARY COMMENTS**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) Extended-Release Tablets 50, 100, 150, 200, and 250 mg.

We also refer to your October 15, 2010, correspondence requesting a meeting to discuss the contents of the Division's October 1, 2010, Complete Response letter and your resubmission strategy for your NDA.

This material consists of our preliminary responses to questions from your October 18, 2010, meeting package and any additional comments in preparation for the discussion at the meeting scheduled for November 9, 2010, 9:30 – 10:30 AM, at the FDA White Oak campus, Building 22, Room 1309, between J & J and the Division of Anesthesia and Analgesia 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 (please contact me to do so). 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. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try

to do so if possible. If any modifications to the development plan or additional questions for which you would like Division feedback arise before the meeting, contact me to discuss the possibility of including these items for discussion at the meeting.

Below are the questions from your October 18, 2010, briefing package in italicized font and the Division's preliminary responses in bolded font.

*CHEMISTRY, MANUFACTURING, AND CONTROLS*

*Question 1. Does the Agency agree with our revised dissolution specifications? If it is not possible to provide an assessment of the specifications at this time, does the Agency agree with the approach we have taken in setting the specifications?*

**FDA Response:**

**We agree in general with the time points you have selected. In addition, the proposed specifications seem appropriate; however, their acceptability will be decided upon review of the submission of the complete response.**

*BIOPHARMACEUTICAL DEVELOPMENT AND CLINICAL PHARMACOLOGY*

*Question 2. Does the Agency agree that bioequivalence has been established for the 4 dosage strengths of the therapeutic dose range for tapentadol ER (TRF), i.e., 100, 150, 200, and 250 mg?*

**FDA Response:**

**Based on the information presented in the meeting package, it appears that bioequivalence (BE) has been established for the 4 strengths (i.e., 100, 150, 200, and 250 mg) of the tapentadol ER tablet. However, the acceptance of the study results will be a review issue.**

*Question 3. Does the Agency agree that a biowaiver request for the tapentadol ER intermediate strengths (100, 150, and 200 mg), that would include in vitro comparative dissolution profile data and  $f_2$  calculations, is not needed as bioequivalence studies have been conducted with the intermediate strengths and the study reports for these bioequivalence studies will be included in our response to the Complete Response Letter?*

**FDA Response:**

**Yes, we agree that a biowaiver request with supporting information for Tapentadol ER intermediate strengths (i.e., the 100, 150, and 200 mg) is not required provided that the Agency finds acceptable the in vivo BE studies conducted with these strengths in support of the bridging between the to-be-marketed formulation and the pilot/registration formulation.**

*CLINICAL AND STATISTICAL*

*Question 4. Does the Agency agree that approval for the tapentadol to-be-marketed 50-mg TRF tablet could be granted based on the results of Study PAI-1059/HP82 and the following rationale: (i) the 50-mg dose is intended to be used only during initial titration, (ii) serum*

*tapentadol concentrations achieved with the 50-mg titration dose do not exceed the concentrations achieved with therapeutic doses (100 to 250 mg) of the tapentadol to-be-marketed TRF formulation, (iii) comparable safety profiles have been documented with the 50-mg to-be-marketed TRF and PR2 Phase 3 study formulations, (iv) a cross-study comparison demonstrated that the tapentadol to-be-marketed TRF formulation exhibits linear and predictable pharmacokinetics across the entire dose range (50 to 250 mg)?*

**FDA Response:**

**The results presented in the meeting package indicate that to-be-marketed 50 mg TRF tablet is NOT bioequivalent (C<sub>max</sub> 90% CI: 123 – 135) to Phase 3 PR2 formulation.**

**However, the 50 mg tablet could potentially be approved after review of the rationale proposed above, including the data supporting the safety profile and the pharmacokinetics of the TRF formulation.**

*Question 5. Does the Agency agree with the contents of the proposed Complete Response Safety Update of NDA 200533?*

**FDA Response:**

**The contents of the proposed Complete Response Safety Update are acceptable.**

*Question 6. Does the Agency concur that the final Clinical Study Reports for Studies PAI-3014/KF16 and PAI-3020/KF41 described in the 4-Month Safety Update do not need to be submitted with the Complete Response Safety Update?*

**FDA Response:**

**Since the final clinical study reports for Studies PAI-3014/KF16 and PAI-3020/KF41 were submitted to IND 61,345, you do not need to resubmit them with the Complete Response Safety Update.**

*Question 7. Does the Agency agree with the Sponsor's plan to present ongoing clinical study data in a manner similar to that previously presented in the Integrated Summary of Safety of NDA 200533 and the 4-MSU?*

**FDA Response:**

**Yes, your plan is acceptable.**

*Question 8. For the tapentadol ER Complete Response Safety Update, are the proposals for the submission of post-marketing experience on tapentadol drug safety acceptable to the Agency?*

**FDA Response:**

**Yes, your proposal is acceptable.**

*Question 9. The Sponsor proposes to provide patient profiles and the analysis dataset for the completed Phase 3 Study PAI-3010/KF18 only. Does the Agency agree that this is acceptable?*

**FDA Response:**

**Yes, your proposal is acceptable.**

*Question 10. For all completed studies, the Sponsor will provide case report forms (CRFs) and narratives for all subjects who died, had a serious adverse event, or discontinued study medication due to an adverse event as outlined in the briefing document. Does the Agency agree with this approach?*

**FDA Response:**

**Yes, this approach is acceptable.**

*REGULATORY*

*Question 11. Does the Agency agree with the proposed content of the submission that will be provided in response to the 01 October 2010 Complete Response Letter?*

**FDA Response:**

**Yes, the proposed content is acceptable. Additionally, Module 2 should contain Summaries of Clinical Pharmacology and Biopharmaceutics, including formulation information used in bioequivalence studies.**

*Question 12. Will the scheduling of the Advisory Committee meeting for the tapentadol ER tablet (to-be-marketed TRF formulation) be contingent upon the date of the Complete Response re-submission?*

(b) (4)

**FDA Response:**

**We are reconsidering the need for this Advisory Committee meeting and will make a final decision upon our review of your complete response.**

You should provide me 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) 796-1183.

Sincerely yours,

*{See appended electronic signature page}*

Dominic Chiapperino, Ph.D.  
Senior Regulatory Health Project Manager  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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DOMINIC CHIAPPERINO  
11/08/2010



NDA 200533

**MEETING REQUEST GRANTED**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) Extended-Release Tablets, 50, 100, 150, 200, and 250 mg.

We also refer to your October 15, 2010, correspondence requesting a meeting to discuss your resubmission strategy for a second cycle review of NDA 200533, following our Complete Response action on October 1, 2010. Your October 18, 2010 meeting briefing package is also acknowledged and under review. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

**Date:** November 9, 2010  
**Time:** 9:30 – 10:30 AM  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room 1309  
Silver Spring, Maryland 20903

**CDER participants:**

Bob A. Rappaport, M.D., Director, Division of Anesthesia and Analgesia Products (DAAP)  
Rigoberto Roca, M.D., Deputy Director, DAAP  
Ellen Fields, M.D., Medical Team Leader, DAAP  
Jin Chen, M.D., Medical Officer, DAAP  
Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAP

Suresh Doddapaneni, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCP2)  
David J. Lee, Ph.D., Clinical Pharmacologist, DCP2  
Dionne Price, Ph.D., Team Leader, Division of Biostatistics II (DB2)  
Yan Zhou, Ph.D., Biostatistics Reviewer, DB2  
Danae Christodoulou, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)  
Craig Bertha, Ph.D., Pharmaceutical Quality Reviewer, ONDQA  
Sandra Suarez Sharp, Ph.D., Biopharmaceutics Reviewer, ONDQA  
Patrick Marroum, Ph.D., Supervisory Biopharmaceutics Reviewer, ONDQA  
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, ONDQA

Please e-mail me any updates to your attendees at [Dominic.Chiapperino@fda.hhs.gov](mailto:Dominic.Chiapperino@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 defined as any non-U.S. citizen or dual citizen who does not have 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.

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 either of the following numbers to request an escort to the conference room: Dominic Chiapperino, at X6-1183, or Cynthia Olsen, DAAP secretary, at X6-1602.

If you have any questions, call me at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Dominic Chiapperino, Ph.D.  
Senior Regulatory Health Project Manager  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
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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DOMINIC CHIAPPERINO  
10/29/2010



NDA 200533

**ADVICE/INFORMATION REQUEST**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended release tablets 50, 100, 150, 200, and 250 mg.

We also refer to your submissions dated November 30, 2009, and June 21, 2010.

We are reviewing the proposed Risk Evaluation and Mitigation Strategy (REMS) section of your submission and have the following comments and information requests. Please note that these are interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application. In order to continue our evaluation of your NDA, we request a prompt written response.

1. Regarding the proposed REMS document, please see Appendix A (Appendix B – clean version) to view revisions to the proposed REMS. These revisions are consistent with current Agency standards for REMS for long-acting opioid analgesics for chronic pain.
2. Regarding the Goals stated in the REMS, these have been reviewed and are acceptable.
3. Regarding the Medication Guide, which will be dispensed with each Nucynta ER prescription in accordance with 21 CFR 208.24, detailed information on the distribution and dispensing of the Medication Guide has been deleted from the REMS document, and should be included in the REMS supporting document. Specific comments on the Medication Guide will be provided in a separate communication.

4. Regarding the Elements to Assure Safe Use:
  - a. See Appendix C (Appendix D for clean copy) for revisions to the Dear Healthcare Professional Letter.
  - b. Rename the Nucynta ER prescribing brochure to the *Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER*. A brochure may be perceived as promotional material, it may not be readily apparent that it contains important safety information.
  - c. Include the following items under elements to assure safe use:
    - Dear Healthcare Professional Letter,
    - Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER, and
    - Nucynta ER Educational Confirmation Form
  - d. The Dear Healthcare Professional letter should be available on the Ortho-McNeil-Janssen Pharmaceuticals, Inc. website for a time period of one year after the date of the ‘initial’ mailing to targeted healthcare professionals.
  - e. Replace the symbol "C-II", and include the following statement: "NUCYNTA ER is a Schedule II controlled substance (C-II)." Alternatively, you can add the symbol next to the first sentence in the fourth paragraph: "Nucynta ER contains tapentadol, which is a morphine-like opioid agonist and a Schedule II controlled substance (C-II) with an abuse liability similar to other opioid agonists, legal or illicit."
  - f. The Dear Healthcare Professional letter mentions a Nucynta ER Healthcare Professional Training Program Kit. To be consistent with terminology in (b), rename the kit to the “Healthcare Professional Educational Program Kit.” Provide an explanation of the purpose and the educational content of the kit in the proposed REMS and REMS supporting document. List all the components included in the kit.
  - g. Remove the highlights of the Prescribing Information as an attachment to the Dear Healthcare Professional letter. The highlights do not provide detailed safety information. Instead, attach the prescribing information (PI), which includes a section of highlighted safety information.
  - h. The initial mailing of the prescriber education material should include the following:

- Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER (formerly named Nucynta ER Prescribing Brochure),
  - Nucynta ER Prescribing Information,
  - Medication Guide, and
  - Educational confirmation form with survey questions.
- i. [REDACTED] (b) (4) from the REMS. If so desired, these letters can be distributed outside of the REMS.
- j. Make the following revisions to the Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER (formerly named Nucynta ER Prescribing Brochure):
- i. Revise the guide by providing information in a more succinct manner by using bulleted text and subheadings.
  - ii. Revise to include these specific sections:
    - purpose statement for the brochure,
    - indication,
    - contraindication,
    - adverse effects (risk of respiratory depression, additional side effects)
    - addictive disorder and physical dependence
    - appropriate dosing and administration
    - patient selection/patient counseling
- k. For consistency with other extended-release opioid REMS, rename the [REDACTED] (b) (4) to the Nucynta ER Education Confirmation Form. See Appendix E for revisions (Appendix F for clean copy).
5. Regarding the Implementation System, because Nucynta ER can be approved without elements to assure safe use, as described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system is not required.
6. Regarding the Timetable for Submission of Assessment, the proposed timetable for submission of assessments is acceptable.
7. Regarding the REMS Supporting Document:
- a. All changes in the REMS should also be addressed in the REMS Supporting Document.
  - b. In the section titled “information for assessment”, include the following:

- An evaluation of patients' understanding of the serious risks of Nucynta ER,
  - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24,
  - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance,
  - A report on the status of the training program for healthcare providers,
  - An evaluation of health care providers' awareness and understanding of the serious risks associated with Nucynta ER,
  - Specify measures used to increase awareness of surveys,
  - An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction,
  - An analysis to evaluate utilization patterns including use in non-opioid tolerant patients, and
  - With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.
8. Submit for review a detailed plan that will be used to evaluate patients', and prescribers' understanding about the safe use of Nucynta ER. The proposed plan does not need to be submitted for FDA review prior to approval of the REMS; however, it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the knowledge about the risks associated with and safe use of Nucynta ER.
9. Regarding the Survey Methodology:
- a. Recruit respondents using a multi-modal approach. For example, respondents could be recruited, through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line. Explain how often non-respondent follow-up or reminders will be performed. If an incentive or honorarium is used, please provide details on what is offered and the estimated dollar value. Explain how recruitment sites will be selected.
  - b. Define the sample size and confidence intervals associated with that sample size.
  - c. Define the expected number of people that will be surveyed to obtain the proposed sample size, and how the sample will be determined (selection criteria).
  - d. The sample should be demographically representative of the population who use the drug (patients), and prescribe the drug (doctors).

- e. If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, and geographically.
- f. List the inclusion criteria for patients and prescribers. For example, eligible patient respondents must be:
  - Age 18 years or older,
  - Currently taking Nucynta ER or have taken the drug in the past 3 months,
  - Not currently participating in a clinical trial involving Nucynta ER, and
  - Not a healthcare provider.

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

- g. Explain how surveys will be administered and the intended frequency. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online, e-mail, in writing, by mail, over the phone, or in person. Explain how surveyors will be trained.
- h. Explain how you would control for limitations or bias that may be associated with the methodology and survey instruments.
- i. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey. Potential respondents should be told that their answers will not affect their ability to take (patients) or prescribe (doctors) Nucynta ER, and that their answers and personal information will be kept confidential and anonymous.
- j. Respondents should not be eligible for more than one wave of the survey.
- k. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). Data may be stratified by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments that were utilized.

10. Regarding the Assessment of Patients' Knowledge:

- a. The assessment is not intended to evaluate patient comprehension of the Medication Guide. Rather, the assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of Nucynta ER. Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed,

respondents should not be offered an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

- b. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
- c. The patient knowledge survey should include questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Nucynta ER?" section of the Medication Guide.

The risk-specific questions should not be biased or leading and multiple choice questions should include instructions to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

- d. Order the patient questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

- e. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
- f. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Nucynta ER. The Medication Guide is a paper handout that contains important information about the risks associated with use of Nucynta ER and how to use Nucynta ER safely. Medication Guides always include the title "Medication Guide" followed by the word Nucynta ER and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I

should know about Nucynta ER,” “What is Nucynta ER,” and “Who should not take Nucynta ER.”

- g. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

Who gave you the Medication Guide for Nucynta ER? (Select all that apply)

- a) My doctor or someone in my doctor’s office
- b) My pharmacist or someone at the pharmacy
- c) Someone else - please explain: \_\_\_\_\_
- d) I did not get a Medication Guide for Nucynta ER.

Did you read the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did you understand what you read in the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did someone offer to explain to you the information in the Medication Guide?

- a) Yes, my doctor or someone in my doctor’s office
- b) Yes, my pharmacist or someone at the pharmacy
- c) Yes, someone else – please explain: \_\_\_\_\_
- d) No

Did you accept the offer? Yes or No

Did you understand the explanation that was given to you?

- a) All,
- b) Most,
- c) Some,
- d) None

Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by you prior to your submission to the FDA.

11. Regarding the Assessment of Healthcare Providers' (prescribers) Knowledge:

- a. The assessment should evaluate how effective the REMS is in achieving the goal(s), by evaluating healthcare providers' knowledge of:
  - the serious risks associated with use of Nucynta ER,
  - how to properly prescribe Nucynta ER, and
  - how to properly monitor for the serious risks associated with the use of Nucynta ER.

The assessment is not intended to assess healthcare providers' comprehension of the educational materials.

Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

- b. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
- c. The healthcare provider knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials. Questions should not be biased or leading, and multiple choice questions should include instructions to "select all that apply." Each question should have an "I don't know" answer option. The order of the multiple choice responses should be randomized on each survey.
- d. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

- e. Use the following (or similar) questions to assess receipt and use of the educational materials.

Prior to today, which of the following were you aware of or received with regard to Nucynta ER? (Select all that apply)

<b>Educational Material</b>	<b>Aware</b>	<b>Received</b>
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Professional Letter	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

Did you read the Full Prescribing Information?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Full Prescribing Information

Did you read the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Medication Guide

Did you read the Dear Healthcare Professional Letter?

- a) All,
- b) Most,
- c) Some,
- d) None
- e) I did not receive the Nucynta ER Dear Healthcare Professional Letter

Did you read the Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER?

- a) All,
- b) Most,
- c) Some,
- d) None

- e) I did not receive the Healthcare Professional Educational Program: A Guide for Healthcare Professionals Who Prescribe or Dispense Nucynta ER.

Do you have any questions about any of the educational materials related to Nucynta ER? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by you prior to your submission to the FDA.

12. Remove all trademark symbols from the REMs and REMs supporting document except for the trademark symbols after the initial use of the trade name in the REMS and REMS supporting document.
13. Submit revisions for the proposed REMS with appended materials, the REMS Supporting Document, and all other materials in WORD format. It is preferable that the entire REMS and appended materials be a single WORD document. Please provide a track changes and clean version of all revised materials and documents.

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. Additional revisions maybe needed so that the REMS and REMS supporting documents are consistent with the final labeling.

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 Dominic Chiapperino, Regulatory Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

- Appendix A - Proposed REMS with track changes
- Appendix B - Proposed REMS, clean copy
- Appendix C - Dear Healthcare Professional Letter, with track changes
- Appendix D - Dear Healthcare Professional Letter, clean copy
- Appendix E - Nucynta ER Educational Confirmation Form with track changes.
- Appendix F - Nucynta ER Educational Confirmation Form, clean copy

33 Page(s) of Draft REMS has been Withheld in Full as  
B4 (CCI/TS) immediately following this page

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/s/

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PARINDA JANI  
09/21/2010



NDA 200533

**GENERAL ADVICE**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended release tablets.

We also refer to your submissions dated March 11, April 30, May 13, June 4, and July 23, 2010.

We note the questions to the Division in your June 4, 2010, submission, in which you proposed new bioequivalence (BE) studies to support the bridging between the to-be-marketed (TBM) tamper-resistant formulation (TRF) of tapentadol extended release tablets and the formulation of tapentadol extended release tablets used in pivotal clinical trials (i.e., PR2). The Division issued a Discipline Review letter on August 11, 2010, to inform you of the deficiencies identified by the biopharmaceutics review team after completing their review of the above referenced submissions. The completed biopharmaceutics review of your application, as amended, permits us to now provide responses to your questions in the June 4, 2010 submission, as follows:

*Question 1. Does the Agency agree that the proposed BE studies in the fasted state comparing TBM TRF of 150 and 200 mg to Phase 3 PR2 will complete the bridge for these two dosage strengths?*

FDA Response:

No, we do not agree. The composition of the 50 mg strength is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths (i.e., 150, 200, and 250 mg). Therefore, to support all the dosage strengths (i.e., 50, 100, 150, 200, and 250 mg) of TBM TRF manufactured at the Gurabo site, you need to conduct and submit the results from the following studies:

1. In vivo BE studies (TBM TRF to Phase 3 PR2) of the 50 and 250 mg strengths under fasting conditions; and

2. Dissolution profile comparisons with similarity  $f_2$  testing (i.e., 50 mg vs. 100 mg; 250 mg vs. 150 mg; and 250 mg vs. 200 mg) in at least three dissolution media (e.g., pH 1.2, 4.5 and 6.8).

Additional comment:

You were advised in our August 11, 2010, letter that your dissolution specifications and acceptance criteria, based on IVIVC models, would need to be revised. To support your revised dissolution acceptance criteria, submit the following information:

- Revised dissolution specifications for all the proposed strengths of TBM TRF tapentadol ER tablets;
- Dissolution profile data (raw data and mean values) from all the batches tested in the above BE studies;
- Data from the BE studies bridging the clinical trial formulations to the TBM TRF; and
- Dissolution profile comparison data.

*Question 2. Does the Agency agree that no further exploration of bioequivalence and food effect beyond the data obtained from the following studies is necessary for bridging between the PR2 formulation used in clinical studies and the TBM TRF?*

- PAI-1055/HP67 (Relative bioavailability of the TBM TRF and PR2 250 mg tablets, fed),
- PAI-1034/HP42 (Bioequivalence of TRF registration and PR2 50 mg tablets, fasted),
- PAI-1046/HP61 (Bioequivalence of TRF registration and PR2 100 mg tablets, fasted), and
- PAI-1033/HP31 (Bioequivalence of TRF registration and PR2 250 mg tablets, fasted).

FDA Response:

Refer to our response to Question 1. The *in vivo* BE studies should be performed under fasting conditions. It is not necessary to assess BE under fed conditions.

*Question 3. Does the Agency agree that the 2 above points enables the Sponsor to commercialize all 5 dose strengths (50, 100, 150, 200, and 250 mg) of TRF manufactured at the commercial manufacturing site in Gurabo upon approval?*

FDA Response:

No, we do not agree. Refer to our response to Question 1.

*Question 4. Final Clinical Study Reports for the pivotal BE studies at 150 and 200 mg will be available in August 2010. Given that submission of these reports will occur after Month 7 of the review cycle, would the Agency consider granting an extension of the PDUFA date for NDA 200533?*

FDA Response:

Pivotal BE studies need to be performed for 50 mg and 250 mg strengths. Refer to our response to Question 1. An extension of the PDUFA date, as provided for in 21CFR Part 314.60(b)(1), would be considered if results from pivotal BE studies are submitted within the last 90 days of the review cycle. However, an extension may not be granted if it is likely that the extension period would not be sufficient to review the submitted data and complete the required inspection(s).

*Question 5. Does the Agency agree that additional BE studies are required for 50, 100, and 250 mg and that these study reports can be submitted in a staggered fashion to the NDA during a cycle extension, if granted?*

FDA Response:

Refer to our response to Questions 1 and 4. Although you may submit additional study reports during a cycle extension, if granted, the remaining time in the extension may or may not be adequate to review the data and perform any required inspection(s).

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

Sincerely,

*{See appended electronic signature page}*

Bob. A. Rappaport, M.D.  
Director  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL
NDA-200533	GI-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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BOB A RAPPAPORT  
08/12/2010



NDA 200533

**DISCIPLINE REVIEW LETTER**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended release tablets 50, 100, 150, 200, and 250 mg.

We also refer to your submissions dated March 11, April 30, May 13, June 4, and July 23, 2010.

We note the teleconference held between FDA staff and Johnson and Johnson (J&J) on April 21, 2010, as reflected in the meeting minutes submitted by J&J on May 13, 2010. One of the important outcomes of the teleconference, reflected in J&J's minutes, was that the FDA biopharmaceutics review team conveyed to J&J its finding that the In-Vitro/In-Vivo Correlation (IVIVC) models submitted with the NDA were inadequate to support the bridging strategy between clinical study batches and the to-be-marketed (TBM) tamper resistant formulation (TRF).

We also note your submission dated June 4, 2010, containing proposals and descriptions of new bioequivalence studies and your questions to the Division regarding these proposals. We will address these questions in a separate communication that provides our responses and recommendations.

Our review of the biopharmaceutics section of your NDA submission, as amended, is complete and we have identified the following deficiencies.

Deficiencies:

1. Your proposed IVIVC models do not support the bridging of the clinical study batches to the TBM TRF.
2. The re-constructed IVIVC models using individual plasma concentrations are not acceptable for the following reasons:

- The models submitted on July 23, 2010, still include a mathematical term that has no mechanistic foundation and, therefore, are not acceptable.
  - The models using the individual subject concentrations failed the external validation, indicating a lack of robustness.
3. The proposed dissolution acceptance criteria for TBM TRF tapentadol ER tablets were based on the proposed IVIVC models. Because these models were not accepted, these dissolution acceptance criteria will need to be revised.

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 Dominic Chiapperino, Regulatory Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL
NDA-200533	GI-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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PARINDA JANI  
08/11/2010



NDA 200533

**MEETING DENIED**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nucynta ER (tapentadol) extended release tablets.

We also refer to your May 13, 2010, correspondence requesting a type A meeting to discuss new bioequivalence studies intended for bridging between tapentadol drug product formulations. We are denying the meeting because the issues and questions presented in the meeting request submission do not warrant a type A meeting. The Division is currently considering the information provided in the May 13<sup>th</sup> submission, and the impact these concerns may have upon the review cycle for NDA 200533, and will respond to your questions in writing and within a reasonable period of time.

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

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	GI-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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PARINDA JANI  
05/27/2010



NDA 200533

**REMS NOTIFICATION LETTER**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRADENAME (tapentadol) extended-release (ER) tablets.

We also refer to your proposed Risk Evaluation and Mitigation Strategy (REMS) voluntarily submitted on November 30, 2009, received December 1, 2009.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh its risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for tapentadol ER to ensure that the benefits of the drug outweigh its risks of abuse, misuse, and overdose, as well as the risk of use of tapentadol ER in non-opioid-tolerant individuals.

As you know, we are considering what REMS elements should be implemented for a number of opioid products, including modified-release opioids, to address the risks of abuse, misuse, overdose, and addiction and the risks of use in non-opioid-tolerant individuals. Once we determine the necessary elements of the class-wide REMS, we will notify you in writing and you will be required to submit a modified REMS incorporating those elements.

We are in the process of reviewing your proposed REMS provided in your NDA submission dated November 30, 2009. We believe that the Medication Guide and the communication plan will not be adequate to ensure adequate training of healthcare providers to address the risks of abuse, misuse, and overdose, as well as the risk of use of tapentadol ER in non-opioid tolerant individuals, and to prevent the occurrence of serious adverse events associated with those risks. Therefore, we have determined that the REMS for tapentadol ER must contain an element to

assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), to ensure that the benefits of the drug outweigh the risks described above.

Based on our current understanding of the risks, your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that tapentadol ER poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of tapentadol ER. FDA has determined that tapentadol ER is a product for which patient labeling could help prevent serious adverse effects, and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use tapentadol ER. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed tapentadol ER.

**Elements to Assure Safe Use:** We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of tapentadol ER. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate these serious risks. Your REMS must include tools to manage these risks, including at least the following:

A plan to ensure that tapentadol ER will only be prescribed by healthcare providers who have particular training about the information described below [under 505-1(f)(3)(A)]. At a minimum, the plan shall require that:

- (a) Healthcare providers are trained about:
  - (i) Proper patient selection
  - (ii) Appropriate dosing and administration
  - (iii) General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
  - (iv) The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including tapentadol ER
  - (v) The risks of tapentadol ER including:
    - 1. The risk of overdose caused by exposure to an essentially immediate-release form of tapentadol due to broken, chewed, crushed, or dissolved tapentadol ER
    - 2. The risk of addiction from exposure to tapentadol ER
    - 3. The risk of use in non-opioid-tolerant individuals
  - (vi) Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances
  - (vii) The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read it.
- (b) Healthcare providers are retrained periodically, at a specified interval.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequently than every 6 months for the first two years and annually thereafter. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for tapentadol ER. Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but may not be limited to:

- a. An evaluation of patients’ understanding of the serious risks of tapentadol ER.
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- d. A report on the status of the training program for healthcare providers.
- e. An evaluation of healthcare providers’ awareness and understanding of the serious risks associated with tapentadol ER (for example, through surveys of healthcare providers).
- f. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
- g. An analysis and summary of surveillance and monitoring activities for abuse, misuse and overdose, and any intervention taken resulting from signals of abuse, misuse, and overdose.
- h. A claims study to evaluate tapentadol ER utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.
- i. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS.

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 200533  
PROPOSED REMS - AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Dominic Chiapperino, Regulatory Project Manager, at 301-796-1183.

Sincerely,

*{See appended electronic signature page}*

Larissa Lapteva, M.D., M.H.S.  
Deputy Director for Safety  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: REMS Template A and B

## **Appendix A- REMS Template**

<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

### **PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOAL(S):**

List the goals and objectives of the REMS.

#### **II. REMS ELEMENTS:**

##### **A. Medication Guide or PPI**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

##### **B. Communication Plan**

*If a Communication Plan is included in the proposed REMS, include the following:*

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

##### **C. Elements To Assure Safe Use**

*If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:*

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

#### **D. Implementation System**

*If an Implementation System is included in the proposed REMS, include the following:*

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

#### **E. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

## **Appendix B**

### **REMS Supporting Document Template**

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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LARISSA LAPTEVA  
04/22/2010

## Chiapperino, Dominic

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**From:** Chiapperino, Dominic  
**Sent:** Friday, March 19, 2010 11:52 AM  
**To:** 'Dusek, Kathleen [PRDUS]'  
**Subject:** Information Request, IVIVC models

Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs  
Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.

Dear Katie,

Please refer to your NUCYNTA (tapentadol) ER New Drug Application (NDA 200533) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Our CMC/Biopharmaceutics reviewer has identified a need for some additional information:

We noticed that your IVIVC models proposed for tapentalol ER tablets contain [REDACTED] (b) (4)

[REDACTED] We recommend that you remove this term and construct and validate the model without this correction factor, and then submit the revised model to the NDA for our review. The reason for this request is that IVIVC models are used in place of bioequivalence testing, which is usually conducted under fasting conditions unless it is indicated that the drug should be taken with food.

If you have any questions about this information request please call me.

Sincerely,

Dominic Chiapperino, Ph.D.  
*Senior Regulatory Health Project Manager*  
*FDA, Center for Drug Evaluation and Research*  
*Division of Anesthesia and Analgesia 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*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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DOMINIC CHIAPPERINO  
04/16/2010  
Archiving email sent Mar. 18, 2010

## Chiapperino, Dominic

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**From:** Chiapperino, Dominic  
**Sent:** Tuesday, April 13, 2010 2:17 PM  
**To:** 'Dusek, Kathleen [PRDUS]'  
**Subject:** Information Request, DSI

Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs  
Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.

Dear Katie,

Please refer to your NUCYNTA (tapentadol) ER New Drug Application (NDA 200533) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

The Division of Scientific Investigations (DSI) has identified the need for some additional information, as follows.

The following requests concern Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) entitled "A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase 3 Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain" and Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD) entitled "A Randomized-Withdrawal Phase III Study Evaluating the Safety and Efficacy of CG5503 Extended-Release (ER) in Subjects with Painful Diabetic Peripheral Neuropathy (DPN)":

**I. Please provide the following information concerning clinical trial data:**

1. Name, address and contact information of all CROs used in the conduct of the clinical trials.
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies.
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.).

**II. Please provide the following information concerning the eDiaries used in each of the trials:**

1. Information concerning the electronic diary including instructions for use provided to subjects and investigators during the trial. Please include a description of support services available to subjects and investigators during the trial.
2. Please document the nature of the data generated by the electronic diary and describe the procedures used by the clinical investigator to collect and review the electronic diary.
3. During the clinical trial, did sites retain the data in paper form or have access electronically? If electronic access, please describe.
4. Data captured on the eCRFs and the eDiaries were provided to the CI on CD(s) at the close of the study. Please state who provided the CD(s) and the contents of the CD(s).
5. Concerning the software:
  - a. Who designed and developed the software?
  - b. Could it be modified, or has it been modified? If so, by whom?
  - c. Has the software been validated? Who validated the software?
  - d. What was the process used to validate the software? How was the validation process documented?
  - e. Were error logs maintained (for errors in software and systems) and do they identify corrections made?
  - f. If data could be modified, how would the sponsor be aware of any changes?
6. Concerning data flow:

- a. Who was authorized to access the system and enter data or change data?
  - b. Is there an audit trail to record changes to subject entries, including who, when, and why the change was made?
  - c. Are there edit checks and data logic checks for acceptable ranges of values?
  - d. How are the data transmitted from the subject to the sponsor or CRO?
7. Concerning computerized system security:
- a. How was system access managed, e.g., access privileges, authorization/deauthorization procedures, physical access controls? Are there records describing the names of authorized personnel, their titles, and a description of their access privileges?
  - b. What methods were used to access computerized systems, e.g., identification code/password combinations, tokens, biometric signatures, electronic signatures, digital signatures?
  - c. How were the data secured in case of disasters, e.g., power failure? Are there contingency plans and backup files?
  - d. Were there controls in place to prevent, detect, and mitigate effects of computer viruses on study data and software?
  - e. Were controls in place to prevent data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software?
  - f. When and how was data accessible to the clinical investigator?
8. Were there written procedures for software validation, data collection, and computerized system security?
9. To facilitate our understanding of how data were transmitted from the eDiary and prepared for submission to the Agency, please provide a flow diagram that tracks the course of data generated by the subject through submission in the NDA. Please also include a diagram that tracks the course of the data to the clinical investigator for archiving at the end of the trial. The diagram should identify who was responsible for each step in the process and should also specify points in dataflow where an audit trail exists.

### III. Request for specific protocol information and site level and subject level data:

For the following protocols and sites: Protocol KF5503/23 (Grünenthal) aka Protocol R331333-PAI-3011 (J&JPRD) entitled “A Randomized Double-Blind, Placebo- and Active-Control, Parallel-arm, Phase 3 Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain” Pamela Amador, M.D. site 49, and Protocol KF5503/36 (Grünenthal) aka Protocol R331333-PAI-3015 (J&JPRD) entitled “A Randomized-Withdrawal Phase III Study Evaluating the Safety and Efficacy of CG5503 Extended-Release (ER) in Subjects with Painful Diabetic Peripheral Neuropathy (DPN)” the following 3 sites:

1. Daniel Whittington, M.D., site 1478
2. Bret Wittmer, M.D., site 1477 and
3. Allan Soo, M.D., site 1460

Please provide the information listed below:

- A. For each protocol, please provide an electronic copy of the protocol and blank eCRF.
- B. Please provide the following site-specific individual subject data (“line”) listings by subject number, from the datasets:
  1. Listings by site and subject, of screened subjects and reason for subjects who did not meet eligibility requirements
  2. Listing by site and subject, of treatment assignment (randomization)
  3. Listings by site and subject, of drop-outs and discontinued subjects with date and reason
  4. Listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
  5. Listings by site and subject, of AEs, SAEs, deaths and dates
  6. Listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation and dates
  7. Listings by site and subject, of the primary endpoint the NRS and the date entered into the diary. Please provide all the data listings that comprised the NRS scores for the primary endpoint, including baseline values.
  8. Listings by site and by subject, of rescue and concomitant medications and dates taken.
  9. Listings by site and by subject, of study drug administration and date dispensed(placebo, active comparator and test article)
  10. Listings by site and subject of SOWS and COWS and the date of the value

Note: Listings 3 through 10 above can be arranged either by subject number numerical order or by subject number numerical order within treatment groups.

**IV. Additional request**

For Protocol KF23, please state the reason why two headaches reported by subjects in the eDiary were not captured as adverse events in the clinical database at Dr. Whittington's site (site number 001478).

If you have any questions about this information request please call me.

Sincerely,

Dominic Chiapperino, Ph.D.  
*Senior Regulatory Health Project Manager*  
*FDA, Center for Drug Evaluation and Research*  
*Division of Anesthesia and Analgesia 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*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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DOMINIC CHIAPPERINO  
04/16/2010  
Archiving email sent Apr. 13, 2010



NDA 200533

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, New Jersey 08560-0200

ATTENTION: Kathleen F. Dusek, RPh, RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) dated November 30, 2009, received December 1, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tapentadol Extended-release Tablets, 50 mg, 100 mg, 150 mg, 200 mg and 250 mg.

We also refer to your December 11, 2009, correspondence, received December 11, 2009, requesting review of your proposed proprietary name, Nucynta ER. We have completed our review of the proposed proprietary name, Nucynta ER and have concluded that this is an acceptable nomenclature strategy for this product. However, in our review of the proposed proprietary name we identified some risk of confusion between Nucynta and Nucynta ER since these products overlap in strength (i.e., 50 mg and 100 mg). Thus, in order to minimize the risk of confusion between Nucynta ER and Nucynta, we recommend at the time of product launch you inform healthcare practitioners about the differences between Nucynta ER and currently marketed Nucynta product, and clearly communicate the dosing differences and frequency of administration for each product.

The proposed proprietary name, Nucynta ER, 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 December 11, 2009, 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 Bola Adeolu, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4264. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dominic Chiapperino at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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CAROL A HOLQUIST  
03/09/2010

## Chiapperino, Dominic

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**From:** Chiapperino, Dominic  
**Sent:** Tuesday, March 09, 2010 3:43 PM  
**To:** 'Dusek, Kathleen [PRDUS]'  
**Subject:** New information request

Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs  
Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.

Dear Katie,

Please refer to your NUCYNTA (tapentadol) ER New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

Our clinical review team and the Controlled Substance Staff have identified a need for some additional information.

For this information request, the treatment groups include double-blind (DB) placebo, DB oxycodone CR, open-label (OL) oxycodone CR, all oxycodone CR, DB tapentadol ER, OL tapentadol ER, and all tapentadol ER. We request that you include datasets for these analyses.

1. Submit an analysis of possible abuse-related MedDRA terms (listed below) by treatment group in the pooled controlled dose adjustment DB and OL Phase 3 studies of tapentadol ER (i.e., Studies KF24, KF11, KF12, and KF23). Include only events that occurred after the initial dose of study medication up until the last day of study medication dosing. Include the following possible abuse-related MedDRA terms (exclude HTN and dementia terms):

Euphoria mood, euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high, high feeling, laughter, elevated mood, mood elevate, elation, feeling abnormal, cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey, feeling drunk, drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged, feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness, dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy, thinking abnormal, abnormal thinking, thinking irrational, wandering thoughts, hallucination, illusions, flashbacks, floating, rush, feeling addicted, inappropriate affect, elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation, somnolence: groggy, groggy and sluggish, groggy on awakening, stupor, mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability, memory loss, amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders, drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders, psychosis, psychotic episode or disorder, hostility, anger, paranoia, confusion, disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain

threshold, loss of a sense of personal identity.

2. Submit two analyses of all MedDRA preferred terms by treatment group in the follow-up period in pooled Studies KF24, KF11, KF12, and KF23. For the first analysis, include only events that started within the following period: the day after the last dose of study medication up until the follow-up visit (i.e., 4 days after the last dose). For the second analysis, include events that started the day after the last dose up until the follow-up telephone call (i.e., 10-14 days after the last dose). For these analyses, exclude patients who entered the open-label extension study.

If you have any questions about this information request please call me.

Sincerely,

Dominic Chiapperino, Ph.D.  
*Senior Regulatory Health Project Manager*  
*FDA, Center for Drug Evaluation and Research*  
*Division of Anesthesia, Analgesia, and Rheumatology*  
*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*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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DOMINIC CHIAPPERINO  
04/16/2010  
Archiving email sent Mar. 9, 2010

**RPM FILING REVIEW**  
**(Including Memo of Filing Meeting)**

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

<b>Application Information</b>	
NDA # 200533	
Proprietary Name: Nucynta ER Established/Proper Name: tapentadol Dosage Form: Tablets Strengths: 50, 100, 150, 200, and 250 mg	
Applicant: Ortho-McNeil-Janssen Pharmaceuticals, Inc. c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Date of Application: November 30, 2009 Date of Receipt: December 1, 2009 Date clock started after UN: N/A	
PDUFA Goal Date: October 1, 2010	
Filing Date: January 30, 2010	Date of Filing Meeting: January 4, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3	
Proposed indication(s)/Proposed change(s): Management of moderate to severe chronic pain	
Type of Original NDA:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): 61,345	

<b>Goal Dates/Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			Listed as Oct. 1, 2010
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X		Emails on Dec. 29, 2009 with CMC reviewer, Craig Bertha, confirming that established name should be corrected to "tapentadol".
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>			X	
<b>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</b>			X	
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Payment received on Nov. 12, 2009
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>Note:</b> 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, please list below:</b>			X																	
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>																
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>			X																	
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested:</b> 3 years  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		Two chiral centers, both specified, so a single diastereomer among four possible.
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index</b> : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X			Some labeling files have links not working, but may only be graphic files, where graphics appear in the PI fine.
<b>Controlled substance/Product with abuse potential</b> : Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i> Dec. 18, 2009	X			
<b>BLAs only</b> : Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #			X	

<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the <b>APPLICANT</b>, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	The submitted field copy certification states that the home district has been notified of the electronic submission to CDER of CMC information.

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			An email was sent on Jan. 14, 2010, to PMHS notifying them of need to schedule time with PeRC Committee.
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			Separate submission received Dec. 11, 2009
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			It will be as soon as filing decision official
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			Need to obtain working Word files
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>			X	

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT IRT consult will be requested.

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> August 24, 2006 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> January 23, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 4, 2010

**NDA #:** 200533

**PROPRIETARY NAME:** NUCYNTA ER Tablets

**ESTABLISHED/PROPER NAME:** tapentadol

**DOSAGE FORM/STRENGTH:** 50, 100, 150, 200, and 250 mg

**APPLICANT:** Ortho-McNeil-Janssen Pharmaceuticals, Inc. c/o Johnson & Johnson  
Pharmaceutical Research & Development, L.L.C.

**PROPOSED INDICATION:** Management of moderate to severe chronic pain

**BACKGROUND:** An NDA for Nucynta (tapentadol) immediate-release oral tablets (NDA 22-304) was approved by FDA on November 20, 2008, indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. This new NDA 200533 is for the extended release formulation of tapentadol.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dominic Chiapperino	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Eric Brodsky	Y
	TL:	Sarah Okada	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	

	TL:	N/A	
Clinical Pharmacology	Reviewer:	David J. Lee	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Yan Zhou	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kathleen Young	Y
	TL:	Adam Wasserman	Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:	TBD	N
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Craig Bertha	Y
	TL:	Danae Christodoulou Prasad Peri	Y Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	TBD	
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey Jeanne Perla Gita Toyserkani Steve Morin	Y N N N
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		N
CSS	Alicja Lerner Lori Love Mike Klein		Y Y Y
CDER/OC	Agnes Plante		Y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> No disciplines reported any problems with electronic submission/format</p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> It was discussed that this NDA did not raise new issues or concerns that would warrant bringing to ALSDAC meeting.</p> <p><b>If no, for an original NME or BLA application, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
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<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> No review issues yet identified.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> No review issues yet identified.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> No review issues yet identified.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> A substantive review of the CMC sections is already completed and a DR letter will be sent, separate from 74-day letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> A new consult will not be needed. The reasons why are documented in the completed CMC review.</p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CMC Labeling Review (BLAs/BLA supplements only)</b></p> <p><b>Comments:</b> Some identified and these will be in a DR letter.</p>	<p>NA</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
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**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Bob Rappaport, MD, Director, DAARP

**21<sup>st</sup> Century Review Milestones (see attached) (optional):** [not attaching]

**Comments:** All milestone meetings and review timelines have been established in accordance with GRMPs and 21<sup>st</sup> Century Review Milestones.

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): CMC issues have been identified, but will be sent in a separate DR letter, not the filing letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

**ACTIONS ITEMS**

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"><li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li><li>• notify DMPQ (so facility inspections can be scheduled earlier)</li></ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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/s/

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DOMINIC CHIAPPERINO  
02/03/2010

PARINDA JANI  
02/04/2010



NDA 200533

**FILING COMMUNICATION**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your new drug application (NDA) dated November 30, 2009, received December 1, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for NUCYNTA (tapentadol) ER Tablets 50, 100, 150, 200, and 250 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is October 1, 2010.

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, mid-cycle, 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 2, 2010.

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. Deficiencies and review issues relating to chemistry, manufacturing, and controls have been identified and will be communicated to you in a separate Discipline Review letter.

## **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 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 Anesthesia, Analgesia, and Rheumatology 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 requests for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if the partial waiver and/or partial deferral requests are denied.

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

Sincerely,

*{See appended electronic signature page}*

Bob A. Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	TAPENTADOL

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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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PARINDA JANI on behalf of BOB A RAPPAPORT  
02/03/2010



NDA 200533

**DISCIPLINE REVIEW LETTER**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
1125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NUCYNTA (tapentadol) ER Tablets 50, 100, 150, 200, and 250 mg.

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

1. Submit the specification for the tapentadol hydrochloride drug substance to the application.
2. Include a test with acceptance criteria for particle size distribution in the drug substance specification, or provide a summary and necessary supportive data to demonstrate that you have assessed whether or not the particle size of the drug substance is critical to the dissolution, solubility, bioavailability, drug product processability, drug product stability, content uniformity, and product appearance.
3. It is stated in section 3.2 of P.2.2 that X-ray powder diffraction analysis of drug product from the registration stability batches (b)(4) Provide a summary of the approximate amounts of the (b)(4) in each of the registration batches and provide a graphical overlay presentation of the corresponding dissolution data collected for each of these batches.
4. Provide the dissolution, content uniformity, and vitamin E assay data from the optimization studies outlined in Table 14 of 3.2.P.2.3.
5. Provide justification for the lack of *any* proposed targets or operating ranges for the (b)(4)

commercial production, as indicated in Table 3 in 3.2.P.2.3. It is unclear that deviating from the proven acceptable ranges used in preparing the commercial site specific stability batches would still produce drug product meeting the critical quality attributes throughout the proposed shelf life. Provide clarification of what (b) (4) parameter targets and ranges will be included in the master batch record (MBR) for each strength (supplying a copy of the (b) (4) section of the MBRs for each strength).

6. Table 3 in 3.2.P.2.3 would appear to indicate that, for future commercial production, (b) (4) include the targets and ranges for these coating parameters in the MBRs for each strength (supplying a copy of the coating section of the MBRs for each strength).
7. Table 3 in 3.2.P.2.3 also indicates that there will be no set target or ranges for the printing speed for future commercial production. (b) (4) Thus, we ask that the MBRs include an allowed operating range for the printing speed such that tablet imprints are reproducible and clear.
8. Provide justification for the absence of in-process tests for (b) (4) uniformity and dissolution.
9. Provide copies of representative infrared spectra used for the identity testing (b) (4)
10. Revise the identity, assay, purity methods (LC-001747, LC-002166, LC-002167, LC-002168, and LC-002169) and the content uniformity method CL-002185 (50 mg strength) to indicate the concentration of (b) (4) in the selectivity solution and the shelf lives and corresponding storage conditions for the reference and sample solutions.
11. Clarify if there is any specific sample preparation necessary for the Near-Infrared method (NI-002130) used for identification of tapentadol in all strengths of the drug product. If so, revise the method accordingly to include these details.
12. The method validation report for the (b) (4) indicated that accuracy was assessed with tablet samples at (b) (4) Provide an explanation of how these different (b) (4) tablet samples were obtained, what strength(s) were represented, and how it was determined that the method was accurate for all five strengths. This was not clear from the information and data in the report.
13. Provide a summary of how the near IR method, NIR-002454, which is used to determine the (b) (4) of all strengths of the tablet drug product, was developed.

14. Revise the near IR method, NIR-002454, so that it contains sufficient detail to allow Agency laboratories to assess and perform the method for regulatory purposes (i.e., materials and equipment, complete instrument parameter settings, system suitability tests and requirements, example spectra, etc.).
15. Regarding the [REDACTED] (b) (4), the five method validation reports for the Near IR method [REDACTED] (b) (4) each indicated that accuracy was assessed with tablet samples with multiple known [REDACTED] (b) (4). Provide an explanation of how these different [REDACTED] (b) (4) tablet samples were obtained for each of the five strengths. This was not obvious from the reports.
16. Provide clarification or explanation of the results of the assessment of the intermediate precision of the near IR method for determination of the tablet [REDACTED] (b) (4) across the strengths. The results from Analyst 2 are observed to be consistently below those of Analyst 1 [REDACTED] (b) (4) based on the mean results.
17. Revise each of the dissolution methods (DU-002150, DU-002151, DU-002152, DU-002153, and DU-002154) such that they indicate the maximum hold time and conditions allowed for collected samples, consistent with the study results in the associated method validation reports.
18. Please be aware that you may be receiving additional comments regarding the dissolution method and associated dissolution acceptance criteria resulting from a review of your application by the biopharmaceutics team.
19. With respect to the justification provided in P.5.6 for the acceptance criterion [REDACTED] (b) (4), you state that, for the development open-dish studies at 25°C/60%RH and 30°C/75%RH, “no effect on chemical stability or dissolution has been observed.” Provide the open-dish study data that support this conclusion.
20. Provide assurance that you are confirming that [REDACTED] (b) (4). This assurance is usually based on certificates of analysis (which could not be found in the application) or based on appropriate physical testing upon your acceptance of this material.
21. Provide the results of a statistical analysis of the [REDACTED] (b) (4) data for the blister packaged drug product stored under long term conditions. The results of this analysis in conjunction with the provision of the requested open-dish stability data supporting the [REDACTED] (b) (4) acceptance criterion, will be used to evaluate the proposed 24-month expiration dating period you are requesting for the blister packaged drug product.
22. Provide a clear color picture of the five dosage forms side-by-side so that the differences between the color, size, shape, and imprints can be evaluated with respect to 21 CFR 206.10.

23. The following preliminary comments pertain to the proposed product labeling.
- a. Revise the DESCRIPTION section of the package insert to comply with 21 CFR 201.57(c)(12), i.e., to state the quantity or proportion of the active ingredient for each strength.
  - b. Revise the DESCRIPTION section to include the pharmacological or therapeutic class of the drug, as per 21 CFR 201.57(c)(12).
  - c. Revise the SPL Drug Listing Data Elements tables' "Basis of Strength" entries to the free-base, i.e., "tapentadol", as is appropriate based on what is indicated in the "Strength" entries.
  - d. Confirm that [REDACTED] <sup>(b)(4)</sup> is an inactive ingredient in the 250 mg strength. If not, make the appropriate modification to the SPL Drug Listing Data Elements table for that strength.

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 Dominic Chiapperino, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200533

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ORIG-1

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ORTHO MCNEIL  
JANSSEN  
PHARMACEUTICA  
LS INC

-----  
TAPENTADOL

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/s/  
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PARINDA JANI  
02/03/2010

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

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

TO:  
**CDER-DDMAC-RPM**  
**ATTN: Wayne Amchin, Mathilda Fienkeng, Twyla Thompson**

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

REQUEST DATE  
**Jan. 22, 2010**

IND NO.

NDA/BLA NO.  
**NDA 200553**

TYPE OF DOCUMENTS  
(PLEASE CHECK OFF BELOW)

NAME OF DRUG  
**NUCYNTA (tapentadol) ER  
Tablets**

PRIORITY CONSIDERATION  
**S**

CLASSIFICATION OF DRUG  
**Type 3**

DESIRED COMPLETION DATE  
(Generally 1 week before the wrap-up meeting)  
**July 20, 2010**

NAME OF FIRM:  
**Johnson & Johnson on behalf of Ortho-McNeil-Janssen  
Pharmaceuticals Inc.**

PDUFA Date: **Oct. 1, 2010**

## 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:**

<\\CDSESUB1\EVSPROD\NDA200533\200533.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

**Mid-Cycle Meeting: April 29, 2010**

**Labeling Meetings: June 21, August 5 and 26, and September 7, 2010**

**Wrap-Up Meeting: July 29, 2010**

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

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

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DOMINIC CHIAPPERINO  
01/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Office of Surveillance and Epidemiology</b> <b>ATTN: Abolade Adeolu, Chris Wheeler, Mary Dempsey</b>		FROM: <b>Division of Anesthesia, Analgesia, and Rheumatology Products -- Dr. Bob Rappaport, M.D.</b> <b>Point-of-contact: Dominic Chiapperino, Ph.D., Senior Regulatory Project Manager, 301-796-1183</b>		
DATE <b>December 28, 2009</b>	IND NO.	NDA NO. <b>200533</b>	TYPE OF DOCUMENT <b>Original submission</b>	DATE OF DOCUMENT <b>Recvd. December 1, 2009</b>
NAME OF DRUG <b>Nucynta (tapentadol) ER</b>		PRIORITY CONSIDERATION <b>S</b>	CLASSIFICATION OF DRUG <b>Type 3</b>	DESIRED COMPLETION DATE <b>August 1, 2010</b>
NAME OF FIRM: <b>Johnson &amp; Johnson on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<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 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 type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
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):		
<b>III. BIOPHARMACEUTICS</b>				
<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		
<b>IV. DRUG EXPERIENCE</b>				
<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		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please review these various sections of this new NDA (#200533, with PDUFA date, Oct. 1, 2010) from a drug safety and risk management perspective. <ul style="list-style-type: none"> <li>• Package Insert labeling</li> <li>• Medication Guide labeling</li> <li>• Carton and Container labeling</li> <li>• Proposed REMS as part of risk management plan (includes Medication Guide and Communication Plan)</li> </ul> This drug product is an opioid schedule II compound (tapentadol) in an extended release formulation. An immediate release formulation is already approved and marketed (NDA 22-304). NDA 200533 is fully electronic (eCTD format) and all files can be found at: <a href="\\CDSESUB1\EVSPROD\NDA200533\200533.ENX">\\CDSESUB1\EVSPROD\NDA200533\200533.ENX</a> Some relevant files are also saved at: < <a href="\\Fdsfs01\ode2\Dominic Chiapperino\NDA 200533 Nucynta-tapentadol-ER">\\Fdsfs01\ode2\Dominic Chiapperino\NDA 200533 Nucynta-tapentadol-ER</a> > This network folder will also be used for shared files/editing. All questions and requests can be sent to Dominic Chiapperino, Senior Regulatory Project Manager. FYI, the assigned Medical Officer reviewing the NDA is Eric Brodsky.				
SIGNATURE OF REQUESTER <b>Dominic Chiapperino (signed electronically)</b>		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

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DOMINIC CHIAPPERINO  
12/29/2009

## REQUEST FOR CONSULTATION

TO (Office/Division):

Controlled Substance Staff (CSS, HFD-009)  
ATTN: Corinne Moody

FROM (Name, Office/Division, and Phone Number of Requestor):

Division of Anesthesia, Analgesia, and Rheumatology  
Products -- Dr. Bob Rappaport, M.D.  
point-of-contact:  
Dominic Chiapperino, Ph.D., Senior Regulatory Project  
Manager, 301-796-1183

DATE December 18, 2009	IND NO.	NDA NO. 200533	TYPE OF DOCUMENT Original Submission NDA	DATE OF DOCUMENT recvd: December 1, 2009
NAME OF DRUG NUCYNTA (tapentadol) ER Tablets		PRIORITY CONSIDERATION No	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE August 1, 2010

NAME OF FIRM: Johnson & Johnson on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

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

#### II. BIOMETRICS

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

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS:**

The Division requests that you please review this new NDA from a controlled substance/abuse potential perspective and provide written feedback by August 1, 2010.

If you require additional items or clarification from the sponsor, please send those requests to DAARP as soon as you are aware of them. Please provide any feedback or deficiencies you wish shared with the sponsor in "letter-ready" format.

This is a fully electronic NDA, available here: \\CDSESUB1\EVSPROD\NDA200533\200533.ENX

Please contact Dominic Chiapperino, RPM, DAARP (HFD-170), at 301-796-1183 with any questions.

SIGNATURE OF REQUESTOR Dominic Chiapperino (electronically signed)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICA LS INC	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

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DOMINIC CHIAPPERINO  
12/18/2009

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<b>REQUEST FOR CONSULTATION</b>	
TO: <i>(Division/Office)</i> Patrick Marroum, Ph.D., Biopharm. Review Expert			FROM: Craig M. Bertha, Ph.D., ONDQA, Div I	
DATE 10-DEC-2009	IND NO. IND 61345	NDA NO. N200533	TYPE OF DOCUMENT Original NDA [505(b)(1)]	DATES OF DOCUMENTS 30-NOV-2009
NAME OF DRUG Nucynta (tapentadol) Extended Release Tablets		PRIORITY CONSIDERATION 3	CLASSIFICATION OF DRUG S	DESIRED COMPLETION Mid-cycle meeting (May 1, 2010)
NAME OF FIRM: Novartis Pharmaceuticals Corporation				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
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>
<b>II. BIOMETRICS</b>				
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	
<b>III. BIOPHARMACEUTICS</b>				
DISSOLUTION BIOAVAILABILITY STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST	
<b>IV. DRUG EXPERIENCE</b>				
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	
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
CLINICAL			PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please see attached. cc: Orig. NDA # 200533 ONDQA/DIV I/CBertha ONDQA/DIV I/PPeri ONDQA/DIV I/DChristodoulou OND/DAARP/PJani				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY <i>(Check one)</i> MAIL    HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

**COMMENTS/SPECIAL INSTRUCTIONS:** Please evaluate the acceptability of the *In vitro – In vivo Correlation* that the applicant claims to have established and validated to predict that the ER registration and the to-be-marketed batches are bioequivalent. The following overview is reproduced from section 2.3 of the Clinical Overview in module 2 of the electronic (eCTD) application.

### **2.3. In vitro - In vivo Correlation**

Two Level A IVIVC models covering high-dose (150 mg to 250 mg) and low-dose (50 mg to 100 mg) tapentadol ER tablet strengths have been established and validated. The models were structurally the same and differed only in the estimated IVIVC parameters (Mod2.7.1\Sec3.2). The Level A IVIVC models are used to predict that ER registration and to-be-marketed batches are bioequivalent (Mod2.7.1\Sec3.4).

In both IVIVC models, that are structurally the same (Mod5.3.1.3\IVIVC report), a pool of independent observations were used (Mod5.3.1.3\IVIVC report\Sec6.2.1) in order to estimate the unit impulse response parameters in the simplest model providing an average of the different responses. Small differences in tapentadol absorption rates may be captured by an FE factor (Mod5.3.1.3\IVIVC report), that was introduced to bridge all studies. The FE factor is a purely empirical estimate to bridge between studies. This factor is applied consistently without regard to formulation and dose strength.

The validity of the Level A IVIVC model was further confirmed by predicting tapentadol serum levels upon multiple dose administration using non-parametric superposition (Mod5.3.1.3\IVIVC report\Sec6.2.5.3). The predicted and observed mean serum concentration-time profiles for the single and multiple dose part of Study PAI-1036/HP38 are in good agreement, supporting the validity of the IVIVC model for multiple dose predictions.

In conclusion, a high- and low-dose Level A IVIVC model was established for tapentadol ER. Both internal and external validation of the model were included to support the validity of both IVIVC models for use in predicting in vivo tapentadol serum concentration-time profiles from in vitro dissolution profiles. This model can be further used to justify dissolution specifications for tapentadol ER (to-be-marketed) tablet formulation and to support future formulation development or modifications.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO-MCNEIL PHARMACEUTICAL, INC.	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

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CRAIG M BERTHA  
12/10/2009

PRASAD PERI  
12/10/2009  
I concur



NDA 200533

**NDA ACKNOWLEDGMENT**

Ortho-McNeil-Janssen Pharmaceuticals, Inc.  
c/o Johnson & Johnson Pharmaceutical  
Research & Development, L.L.C.  
125 Trenton-Harbourton Road, P.O. Box 200  
Titusville, NJ 08560

Attention: Kathleen F. Dusek, R.Ph., RAC  
Associate Director, Regulatory Affairs

Dear Ms. Dusek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: NUCYNTA (tapentadol) ER Tablets 50, 100, 150, 200, and 250 mg

Date of Application: November 30, 2009

Date of Receipt: December 1, 2009

Our Reference Number: NDA 200533

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 January 30, 2010, 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.

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 Anesthesia, Analgesia, and Rheumatology 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>

If you have any questions, call me at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Dominic Chiapperino, Ph.D.  
Senior Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO-MCNEIL PHARMACEUTICAL, INC.	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

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DOMINIC CHIAPPERINO  
12/10/2009

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-----Original Message-----

**From:** Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]

**Sent:** Thursday, February 12, 2009 3:08 PM

**To:** Kaufman, Michael [PRDUS]

**Subject:** RE: Tapentadol ER (IND 61,345): Clarification Request for Questions 23 & 25 of FDA's Written Response to Pre-NDA Meeting Questions

Michael –

See attached.

Matt

---

**From:** Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@its.jnj.com]

**Sent:** Friday, January 30, 2009 8:47 AM

**To:** Sullivan, Matthew

**Subject:** Tapentadol ER (IND 61,345): Clarification Request for Questions 23 & 25 of FDA's Written Response to Pre-NDA Meeting Questions

Dear Matt:

Reference is made to IND 61, 345 and specifically to our 12 December 2008 (Serial No.: 359) correspondence that provided the briefing package for the Tapentadol ER Pre-NDA meeting scheduled for 23 January 2009. Reference is also made to the Division's 21 January 2009 written response to the briefing questions.

Upon detailed review and thorough evaluation, we would like to obtain confirmation or further clarification to the Division's response to Questions 23 and 25, as well as agreement with our proposals noted in the attached document.

We look forward to receiving the Agency's response. Thank you.

**Michael H. Kaufman**

Director, Regulatory Affairs

Johnson & Johnson

Pharmaceutical Research & Development, L.L.C.

Tel: (908) 704-4756

Fax: (908) 722-5113

Email: mkaufman@its.jnj.com

**Confidentiality Notice:** This e-mail transmission may contain confidential or legally privileged information that is intended only for the individual or entity named in the e-mail address. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution, or reliance upon the contents of this e-mail is strictly prohibited. If you have

received this e-mail transmission in error, please reply to the sender, so that Johnson & Johnson can arrange for proper delivery, and then please delete the message from your inbox. Thank you.

*Question 23 For all completed studies, the Sponsor will provide case report forms (CRFs) and narratives for all subjects who died, had a serious adverse event, or discontinued study medication due to an adverse event as outlined in the briefing document. Does the Agency agree with this approach?*

**FDA Response for Question 23:**

Yes we agree. In addition, provide the following information and data related to abuse, misuse, diversion and overdose:

- Descriptions of all reports and details, including narratives, of an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.

**J&JPRD Clarification For Question 23, Bullet 1**

We will provide descriptive and focused narratives for the Tapentadol ER treated subjects describing any known cases of abuse, overuse, or overdose (intentional or unintentional), and will provide information on drug that is lost, stolen, missing or unaccounted for in all Phase 2 and 3 completed and ongoing clinical studies. The cut-off date for the additional information being requested will be the same as outlined in the briefing book and concurred by the Agency in their written response. That is 31 October 2008 for the original NDA and 30 June 2009 for the 4-month safety update report. Does the Agency agree with this proposal?

- Narratives and case report forms for patients that drop out from studies where they were enrolled for reasons that might be coded as “protocol violation”, “lack of efficacy”, “lost to follow up”, “non-compliance to study medication or procedures,” “over compliance” or for “other.”

**J&JPRD Clarification For Question 23, Bullet 2**

The Sponsor would like to clarify the purpose of providing this information to the Agency to ensure that appropriate information is included in the evaluation. The Sponsor plans to provide narratives and case report forms for the Tapentadol ER treated subjects that have discontinued from completed Phase 2 and Phase 3 studies for reasons that might be coded as “protocol violation”, “lack of efficacy”, “lost to follow up”, “subject choice”, “non-compliance to study medication or procedures,” or for “other.” Additionally, the electronic data component from the Phase 3 studies, with reference to pain intensity, will be included in the NDA as a part of the clinical database. Does the Agency agree with this proposal?

**Division Response:**

**Yes, we agree with your proposal for both points.**

*Question 25 Safety data from ongoing clinical studies of any subject, who died or experienced a serious adverse event, will be presented in the ISS by providing the CIOMS report for that case. Does the Agency agree with this proposal?*

**FDA Response for Question 25:**

Yes. In addition, see our response to Question 23.

**J&JPRD Clarification Statement for Question 25:**

As we indicated in our response to Question 23, bullet point 1, we will provide information describing any known cases of abuse, overuse, or overdose (intentional or unintentional), and will provide information on drug that is lost, stolen, missing or unaccounted for in all Phase 2 and 3 completed and ongoing clinical studies.

Narratives and case report forms from ongoing trials (two cancer trials: PAI-3013/KF15 and PAI-3014/KF16, open-label extension study PAI-3010/KF18, and the differentiation study PAI-3020/KF41) will not be included in the NDA for patients who discontinued, because the data are blinded (cancer and differentiation studies) or not completed, cleaned, queried and verified (all ongoing studies). Does the Agency agree with the rationale why we are unable to provide narratives and case report forms for patients who discontinued from ongoing studies?

**Division Response:**

**We agree with your proposal. Provide information on how information about aberrant drug behaviors is defined, identified, collected and evaluated in addition to providing information regarding cases of abuse, misuse and addiction that occur in Phase 3 studies.**

**We are requesting this information to obtain as complete a picture of safety, including abuse and diversion, as possible. In our experience, cases potentially indicating abuse, misuse, withdrawal or drug diversion have been coded as one of the requested codes (“protocol violation”, “lack of efficacy”, “lost to follow up”, “non-compliance to study medication or procedures,” “over compliance” or for “other”), depending on how these terms are defined and interpreted at the study sites.**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 61,345

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
920 Route 202  
Raritan, NJ 08869

Attention: Michael Kaufman  
Director, Regulatory Affairs

Dear Mr. Kaufman:

Please refer to your Investigational New Drug Application (IND) submitted December 1, 2000, received December 2, 2000, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tapentadol HCl tablets.

Attached are the Division's responses to the questions from your December 12, 2008, meeting package for our upcoming meeting, scheduled for January 23, 2009, to discuss your plans for an NDA submission. Your questions are in italics and the Division's responses are in normal text.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Matthew W. Sullivan  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:  
Meeting agenda and responses  
Standard Pre-NDA Comments

**SPONSOR MEETING AGENDA**

**MEETING DATE:** January 23, 2009  
**TIME:** 11:00 am to 12:00 noon  
**LOCATION:** FDA White Oak Campus  
 Silver Spring, MD  
**APPLICATION:** IND 61,345  
**STATUS OF APPLICATION:** Active  
**PRODUCT:** Tapentadol  
**INDICATION:** Treatment of moderate to severe chronic pain  
**SPONSOR:** Johnson and Johnson PRD  
**TYPE OF MEETING:** Type B, Pre-NDA  
**MEETING CHAIR:** Ellen Fields, MD, MPH, Clinical Team Leader, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)  
**MEETING RECORDER:** Matthew Sullivan, M.S., Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Curt Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Ellen Fields, M.D., MPH	Medical Team Leader, DAARP
Elizabeth Kilgore, M.D.	Medical Officer, DAARP
Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology, DAARP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Dionne Price, Ph.D.	Team Leader, Statistics, DAARP
Jon Norton, Ph.D.	Statistics Reviewer, DAARP
Ali Al Hakim, Ph.D.	Chief, CMC Branch II, Office of New Drug Quality Assessment (ONDQA)
Danae Christodoulou, Ph.D.	Pharmaceutical Assessment Lead, Brach II, ONDQA
Craig Bertha, Ph.D.	Chemistry Reviewer, ONDQA
Adam Wasserman, Ph.D.	Supervisor, Pharmacology/Toxicology, DAARP
Kathy Young, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Mike Klein, Ph.D.	Director, Controlled Substances Staff (acting)
Lori Love, M.D..	Medical Officer, Controlled Substances Staff
Patrick Marroum, Ph.D.	Pharmacologist, ONDQA
Jeanne Perla, PhD	Epidemiologist, Division of Risk Management, Office of Surveillance and Epidemiology (OSE)
Afrouz Nayernama	Safety Evaluator, Division of Pharmacovigilance I, OSE
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP

<b>J&amp;J PRD Attendees</b>	<b>Title</b>
Linda Carter	Senior Director, Regulatory Affairs, J&J FDA Liaison Office
Mila Etropolski, M.D.	Senior Director, Clinical Leader
Juergen Haeussler, M.D.	Vice President, Therapeutic Area Head - Pain
Tania Hillmer, M.S.	Manager, Global Regulatory Affairs
Dymphy Huntjens	Senior Scientist, Clinical Pharmacology
Michael Kaufman	Director, Global Regulatory Affairs
Kathy Kelly, M.D.	Director, Medical Leader
Partha Nandy, Ph.D.	Director, Advanced Modeling and Simulation
Akiko Okamoto, Sc.D.	Director, Clinical Biostatistics
<b>Grünenthal GmbH Attendees</b>	<b>Title</b>
Ina Galle, Ph.D.	Head Corporate Regulatory Affairs
Tom Huijbers	Senior Manager, Regulatory Affairs
Bernd Lange, M.D.	International Clinical Project Leader
Horst Weber, M.D., Ph.D.	Global Head of Science

Below are the Division's responses to the questions from your December 12, 2008, meeting package for our upcoming meeting, scheduled for January 23, 2009, to discuss your plans for an NDA submission. Your questions are in italics and the Division's responses are in normal text.

#### **Chemistry, Manufacturing, and Control Questions**

*Question 1 The Sponsor plans to submit 1 executed batch record from 1 representative batch of each tablet strength extreme (50 mg and 250 mg) from the registration stability batches. Does the Agency agree with this approach?*

**FDA Response:**

Yes we agree, as long as the other executed batch records can be made available if necessary.

#### **Nonclinical Pharmacology, Pharmacokinetics, and Toxicology Questions**

*Question 2 In accordance with 21 CFR 314.50(g)(1), the Sponsor plans to cross-reference the relevant nonclinical pharmacology, pharmacokinetics, toxicology, studies and literature contained in Modules 2.4, 2.6, and 4 of the approved tapentadol IR NDA 22-304 to the tapentadol ER NDA. These sections will not be re-submitted with the tapentadol ER NDA. Does the Agency agree with this proposal?*

**FDA Response:**

Yes

*Question 3 Does the Agency agree with the Sponsor's proposal not to include the 8 nonclinical study reports (Attachment 1.1) in the tapentadol ER NDA that have been completed since the submission and subsequent approval of NDA 22-304?*

**FDA Response:**

This is acceptable, as the final study reports were submitted to the IND (61,345) and are available for review.

**Biopharmaceutical Development and Clinical Pharmacology Questions**

*Question 4 Does the Agency agree that the clinical pharmacology and biopharmaceutics studies proposed to be included in the NDA are adequate to support the filing and potential approval of the tapentadol ER NDA?*

**FDA Response:**

The proposed studies are adequate for filing. However, the adequacy of the data will be a review issue.

*Question 5 Does the Agency agree that the IVIVC approach adjusted from the approach discussed at 5 September 2008 TRF Development Meeting, for the bridging of PR2 tablet to the TRF tablet, is still acceptable?*

**FDA Response:**

Your proposal is acceptable.

*Question 6 Does the Agency agree with the proposed population PK analysis outlined in the Briefing Package for tapentadol ER?*

**FDA Response:**

Your proposed population PK analysis is acceptable. We recommend that you provide all datasets used for model development and validation as SAS transport files. A description of each data item should be provided in the define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of modeling steps should be submitted. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and

not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

*Question 7* In accordance with 21 CFR 314.50(g)(1), the Sponsor plans to cross-reference the relevant clinical pharmacology, clinical pharmacokinetics studies and literature contained in Modules 2.7 and 5 of the approved tapentadol IR NDA 22-304 to the tapentadol ER NDA. These sections will not be re-submitted with the tapentadol ER NDA. Does the Agency agree with this proposal?

**FDA Response:**  
Yes

#### Clinical/Statistical Questions

*Question 8*

(b) (4)

**FDA Response:**  
The Division cannot provide a response at this time. Labeling language regarding clinical studies is a review issue.

*Question 9* Does the Agency agree that the Phase 2 and 3 studies listed in this pre-NDA briefing document are sufficient to support the filing and potential approval of the tapentadol ER NDA?

**FDA Response:**  
Yes, they appear adequate to support filing.

*Question 10* For the tapentadol ER NDA, is the proposal for the submission of published literature acceptable to the Agency?

**FDA Response:**  
Yes, the proposal appears acceptable.

*Question 11 Does the Agency agree with the proposed outline of the integrated efficacy analysis discussed in the briefing package?*

**FDA Response:**

You propose to analyze the pooled data from the Phase 3 studies PAI-3008/KF11, PAI-3009/KF12, and PAI-3011/KF23. The main purpose of the integrated summary of efficacy is to explain how the results of the individual studies support the claims being made. A pooled analysis is not usually very helpful in this regard, with the exception of required analyses by age, sex and race. However, in the case of conflicting results, a statistical meta-analysis of the studies may be appropriate.

*Question 12 Does the Agency agree that the ISE will only include Phase 2 and 3 studies conducted for the chronic clinical program that used the tapentadol ER formulation?*

**FDA Response:**

Yes

*Question 13 Does the Agency agree with the proposal to only pool the efficacy results of 3 Phase 3 studies (PAI-3008/KF11 [OA], PAI-3009/KF12 [OA], and PAI-3011/KF23 [LBP]) within the ISE?*

**FDA Response:**

See our response to Question 11.

*Question 14 Does the Agency agree that the proposed statistical analysis plan (SAP) for the ISE for the Phase 3 studies in conjunction with presentation of the individual study data of each clinical Phase 3 study will adequately characterize the efficacy profile of tapentadol ER?*

**FDA Response:**

The proposed presentation of the data is acceptable, keeping in mind our response to Question 11.

*Question 15* Does the Agency agree with the SAP of the differentiation meta-analysis to assess the relative efficacy and safety of tapentadol ER to (b) (4)? The analyses will be included in the SCE/ISE.

**FDA Response:**

The studies are not appropriately designed to characterize the dose-response relationship of the two drugs. Thus, we cannot agree to the statistical analysis plan. See our response to Question 16.

*Question 16*

(b) (4)

**FDA Response:**

(b) (4)

*Question 17* Does the Agency agree with the proposal to integrate only selected Phase 1 studies and to pool safety data from within these Phase 1 studies separately for the tapentadol ER and for the tapentadol TRF formulations?

**FDA Response:**

Yes

*Question 18* Is the proposed plan for pooling and summarization of clinical safety data included in the SAPs acceptable to the Agency?

**FDA Response:**

The proposed pooling and summarization plan is acceptable.

*Question 19* Does the Agency agree that the proposed SAPs for the integrated safety data will adequately characterize the safety profile of tapentadol ER and TRF?

**FDA Response:**

The proposed characterization of the safety profile of tapentadol ER and TRF appears adequate.

*Question 20 Does the Agency agree that the ISS will not include studies using tapentadol IR that were previously submitted in the approved NDA 22-304?*

**FDA Response:**

Yes

*Question 21 The SCS will be provided in Module 2.7.4 and the related ISS will be provided in Module 5.3.5.3 of the NDA. Does the Agency agree with the proposed outline of the integrated safety analyses discussed in the briefing package?*

**FDA Response:**

Yes

*Question 22 The Sponsor proposes to provide patient profiles for Phase 3 studies and not Phase 1 and 2 studies since the complete analysis database for the SCE/ISE and SCS/ISS will be provided in the case report tabulations. In addition, the analysis datasets from the Phase 3 studies will be provided. Does the Agency agree that this is acceptable?*

**FDA Response:**

Yes

*Question 23 For all completed studies, the Sponsor will provide case report forms (CRFs) and narratives for all subjects who died, had a serious adverse event, or discontinued study medication due to an adverse event as outlined in the briefing document. Does the Agency agree with this approach?*

**FDA Response:**

Yes we agree. In addition, provide the following information and data related to abuse, misuse, diversion and overdose:

- Descriptions of all reports and details, including narratives, of an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.
- Narratives and case report forms for patients that drop out from studies where they were enrolled for reasons that might be coded as “protocol violation”, “lack of efficacy”, “lost to follow up”, “non-compliance to study medication or procedures,” “over compliance” or for “other.”

*Question 24 The data from the ongoing Phase 2 and 3 clinical studies will be presented as blinded safety information, including serious adverse events and disposition of subjects as of a cut-off date of 31 October 2008. We do not plan to write*

*individual interim clinical study reports for these clinical studies for the NDA.  
Does the Agency agree with our proposal?*

**FDA Response:**

Yes

*Question 25 Safety data from ongoing clinical studies of any subject, who died or experienced a serious adverse event, will be presented in the ISS by providing the CIOMS report for that case. Does the Agency agree with this proposal?*

**FDA Response:**

Yes. In addition, see our response to Question 23.

*Question 26 The cutoff date for data to be included in the tapentadol ER NDA will be 31 October 2008 (approximately 8 months prior to the submission date). The 4-Month Safety Update (4MSU) will have a proposed data cutoff date of 30 June 2009 (approximately 4 months prior to submission of the 4MSU). Does the Agency agree with the timing of these cutoff dates?*

**FDA Response:**

Yes

*Question 27 Does the Agency agree with the proposed content of the 4-Month Safety Update?*

**FDA Response:**

Yes

*Question 28 Does the Agency agree with the proposed strategy for updating the Medical Dictionary for Regulatory Activities (MedDRA) codes for the integrated safety dataset?*

**FDA Response:**

Yes

**Regulatory Questions**

*Question 29 The Sponsor does not plan to provide Appendix 16.2.6 (individual efficacy response data), 16.2.8 (listing of individual laboratory measurements by*

*subject) and Appendix 16.4 (Individual Patient Data Listings) as defined by the ICH E3 guideline "Structure and Content of Clinical Study Reports" as part of the individual clinical study reports. Instead, datasets will be provided as part of the case report tabulations. Additional information regarding individual subject data listing is provided in Sections 14.4.7.7.2 and 15.5.4.4.2. Is this proposal acceptable to the Agency?*

**FDA Response:**  
Yes

*Question 30 Does the Agency agree with the proposal to submit clinical study reports as a single pdf file and to use the ICH "legacy-clinical-study report" study file tag value?*

**FDA Response:**  
Yes

*Question 31 Is the proposed format and content of the PK electronic datasets that will be provided, acceptable to the Agency?*

**FDA Response:**  
Yes

*Question 32 Does the Agency agree with the proposal to submit individual datasets for each Phase 3 study and pooled safety data of selected Phase 1 studies and comprehensive pooled safety data from all Phase 2 and 3 studies utilizing the ER formulation?*

**FDA Response:**  
Yes

*Question 33 Does the Agency agree that the dataset needs to be split only if it exceeds the file size of 500 MB?*

**FDA Response:**  
Yes

*Question 34 Does the Agency agree with the proposed formatting and naming conventions for the SAS transport files?*

**FDA Response:**

On page 80 of the briefing package, you state, "...the dataset format and naming convention will be similar to those submitted for the NDA 22-304." This is acceptable.

*Question 35 The sponsor plans to submit a draft REMS with the tapentadol ER NDA. Does the Agency agree that the tapentadol ER NDA should include a draft REMS? Does the Agency have any further guidance to provide the Sponsor for consideration when preparing this document?*

**FDA Response:**

We agree that the tapentadol ER NDA should include a draft REMS. Please note that details regarding the contents of the REMS for modified-release opioids are under internal discussion. You will be informed regarding the REMS requirements when they are determined.

*Question 36 According to 21 CFR 54, Sponsors are required to provide certification of financial disclosure in an NDA for any studies the Agency will rely on to establish that a product is effective in a claimed indication. The Sponsor plans to provide financial disclosure information from the 4 Phase 3 efficacy studies (PAI-3008/KF11 [OA], PAI-3009/KF12 [OA], PAI-3011/KF23 LBP], and PAI-3015/KF36 [DPN]) only. All of the other studies conducted to date are supportive and certification of financial disclosure will not be provided. Is this acceptable to the Agency?*

**FDA Response:**

As you note, financial disclosure documents are required for any study used to support the efficacy of an application. If the four studies mentioned are the only ones you would like considered as supportive of efficacy, then your proposal appears acceptable.

*Question 37 Based on the available information the Agency has reviewed for tapentadol ER, particularly the tamper resistant formulation, will the Agency comment on their opinion to consider the tapentadol ER NDA for a priority review?*

**FDA Response:**

The rationale for granting a priority review of a new tamper resistant formulation is that it has the potential to lessen the likelihood of misuse compared to an already approved product. As there are no approved extended-release tapentadol products on the market, there is no basis to support a priority review for this tamper resistant formulation.

*Question 38 Does the Agency anticipate that the tapentadol ER NDA would be the subject of an FDA Advisory Committee meeting for the management of chronic pain?*

**FDA Response:**

The decision as to whether to take the tapentadol ER NDA to an FDA Advisory Committee will be made once the application has been submitted.

*Question 39 Given the Agency's recommendation in the approval letter for NDA 22-304 (tapentadol IR for acute pain) that the product be scheduled under the Controlled Substances Act and that such review is currently ongoing by the Drug Enforcement Administration, the sponsor will not provide an abuse liability assessment update. Does the Agency agree with this proposal?*

**FDA Response:**

We acknowledge that the scheduling for tapentadol IR under the CSA is currently under review at the DEA. Although tapentadol ER potentially introduces additional risks over the immediate-release product, we do not anticipate requesting additional abuse potential data separate from that already requested.

*Question 40 The Sponsor would like to confirm the trademark to be used for the tapentadol ER product. We propose that the ER product be designated with "ER" added to the end of the IR Trademark eg, TRADEMARK-ER. Does the Agency agree with this proposal?*

**FDA Response:**

We cannot provide comments on the proposed proprietary name for the tapentadol tamper resistant formula/extended-release tablet at this time. Tapentadol tablets (NDA 22-304-known as the immediate-release tablets) were approved without a proprietary name and the proposed proprietary name is still under review.

Depending on the final outcome of that review, if the Applicant wants the name 'TRADENAME-ER' for this new formulation, the proposed name 'TRADENAME-ER' will require review. Please refer to the recent guidance document [www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) for more information.

*Question 41 Based on the preliminary draft provided, does the Agency have any suggestions for the Sponsor to consider when preparing the draft label to be included with the tapentadol ER NDA?*

**FDA Response:**

We have no comments for the draft label at this time.

*Question 42* Can the Agency provide any guidance or comments in regard to (b) (4)

[REDACTED]

**FDA Response:**

Safety statements related to the formulation may be appropriate for labeling. The statements must be supported by adequate data and must not infer benefit that has not been adequately demonstrated in clinical trials.

*Question 43* Does the Agency agree that the proposed Phase 1 chewing study to assess the safety and pharmacokinetic parameters of the TRF tablet will provide important safety information for the TRF formulation? As such, does the Agency accept our proposal to amend the pending NDA to submit this Phase 1 study report at the time of the 4-month safety update report?

**FDA Response:**

Please see our response to Question 42 regarding labeling. Additionally, all study reports intended to support this application must be included in the original NDA submission, not in the 4-month safety update. In order for the Agency to comply with the review timelines imposed by FDAAA, all NDA applications must be complete at the time of submission. Material submitted after the original submission may not be reviewed during the review cycle.

## Enclosure 2

### General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 - Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. - Standard analyses and explorations of ECG data.
12. Section 7.1.16 - Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

## Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

## Common PLR Labeling Deficiencies

### **Highlights:**

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
8. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]
11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
12. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
13. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

15. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19. When a subsection is omitted, the numbering does not change.

20. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
24. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-

Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
33. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
34. Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

### **CDISC Data Requests to Sponsors Quantitative Safety and Pharmacoepidemiology Group**

#### **Safety Analysis Plan**

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)). At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- b. Safety endpoints for Adverse Events of Special Interest (AESI)

- c. Definition of Treatment Emergent Adverse Event (TEAE)
- d. Expert adjudication process (Expert Clinical Committee Charter)
- e. Data/Safety Monitoring Committee (DSMC): (Submit charter for FDA review) by
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- g. When unanticipated safety issues are identified the Quantitative Safety Analysis Plan may be amended. Amendments should be filed in accordance with FDA regulations.

### **Study Data Tabulation Model (SDTM) Issues**

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
  - a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at [www.CDISC.org](http://www.CDISC.org) and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.
    - (DV) Protocol deviations
    - (DA) Drug Accountability
    - (PC, PP) Pharmacokinetics
    - (MB, MS) Microbiology
    - (CF) Clinical Findings
  - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
    - Tumor information
    - Imaging Data
    - Complex Inclusion/Exclusion Criteria
3. Variables
  - a. All required variables are to be included.
  - b. All expected variables must be included in all SDTM datasets.
  - c. Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.
  - d. A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.

- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.
  - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
4. Specific issues of note:
- a. SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.
  - b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPQUAL dataset or an ADaM dataset.
  - c. These issues can be addressed through the request for ADaM datasets

#### **Analysis Data Model (ADaM) Issues**

1. Specify which ADaM datasets you intend to submit.
2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.
5. Indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.

#### **General Items**

##### Controlled terminology issues

- a. Use a single version of MedDRA for a submission. Does not have to be most recent version
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements must be addressed.

## Integrated Summary of Effectiveness

Please refer to the Guidance for Industry located at the following web page  
<http://www.fda.gov/cder/guidance/7694dft.pdf>

### Dataset Comments

The Division requests the following for the submitted datasets:

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
  - b. Study/protocol number
  - c. Patient's treatment assignment
  - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
  - e. Dosing at time of adverse event
  - f. Dosing prior to event (if different)
  - g. Duration of event (or start and stop dates)
  - h. Days on study drug at time of event
  - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
  - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - k. Marker for serious adverse events
    1. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the Verbatim term taken from the case report form.
  3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
  4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. Also, for the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates must be formatted as ISO date format.
13. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
14. All datasets must contain the following variables/fields (in the same format and coding):
  - a. Each subject must have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)

15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
17. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.
18. With reference to the table on the following page, note that the HLG and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 61345

-----  
JOHNSON AND  
JOHNSON  
PHARMACEUTICAL  
RESEARCH AND  
DEVELOPMENT LLC

-----  
CG5503

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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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MATTHEW W SULLIVAN  
01/21/2009

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-----Original Message-----

**From:** Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]  
**Sent:** Thursday, October 30, 2008 4:10 PM  
**To:** Kaufman, Michael [PRDUS]  
**Subject:** RE: IND 61,345 (tapentadol): Tapentadol ER eCTD Question

Here you go:

The database format and structure for the Tapentadol ER (chronic pain indication) use the clinical row data model (CRDM) format. This is the same format and structure of the eCTD Tapentadol IR (acute pain indication) NDA currently under review by the Agency. Does the Agency agree that the CRDM format is acceptable for the eCTD Tapentadol ER NDA targeted to be filed in June 2009?

It is acceptable to use the same format and structure of the eCTD Tapentadol IR (acute pain indication) NDA currently under review.

Does the Agency have a date when clinical study datasets for an eCTD submission must only use the Study Data Tabulation Model (SDTM)?

We recommend to submit SDTM in the eCTD submission, but currently there isn't a timeline when eCTD submission must only use the SDTM.

---

**From:** Kaufman, Michael [PRDUS] [mailto:MKAUFMAN@its.jnj.com]  
**Sent:** Monday, October 20, 2008 1:20 PM  
**To:** Sullivan, Matthew  
**Subject:** IND 61,345 (tapentadol): Tapentadol ER eCTD Question

Dear Matt:

We have a question that I need to ask the Agency in advance of our pre-nda meeting for the Tapentadol ER (chronic pain indication) NDA since the response will have direct impact on the eCTD clinical study datasets being created for the eCTD submission. Unfortunately, we can not wait until the January 23rd pre-nda meeting to obtain the Agency's response.

Question:

The database format and structure for the Tapentadol ER (chronic pain indication) use the clinical row data model (CRDM) format. This is the same format and structure of the eCTD Tapentadol IR (acute pain indication) NDA

currently under review by the Agency. Does the Agency agree that the CRDM format is acceptable for the eCTD Tapentadol ER NDA targeted to be filed in June 2009?

Does the Agency have a date when clinical study datasets for an eCTD submission must only use the Study Data Tabulation Model (SDTM)?

Thank you in advance for assistance.

**Michael H. Kaufman**

Director, Regulatory Affairs

Johnson & Johnson

Pharmaceutical Research & Development, L.L.C.

Tel: (908) 704-4756

Fax: (908) 722-5113

Email: mkaufman@its.jnj.com

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014.  
Expiration Date: May 31, 2009  
See OMB Statement on Reverse.

**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**  
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR  
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

2. DATE OF SUBMISSION  
**OCT 07 2008**

3. ADDRESS (Number, Street, City, State and Zip Code)  
920 Route 202  
Raritan, New Jersey 08869

4. TELEPHONE NUMBER (Include Area Code)  
908-704-4756

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)  
CG5503/tapentadol hydrochloride/R331333

6. IND NUMBER (If previously assigned)  
61,345

7. INDICATION(S) (Covered by this submission)  
MODERATE TO SEVERE PAIN

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:  
 PHASE 1  PHASE 2  PHASE 3  OTHER \_\_\_\_\_  
(Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER  
**342**

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)  
 INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)  RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):

- NEW PROTOCOL  
 CHANGE IN PROTOCOL  
 NEW INVESTIGATOR

INFORMATION AMENDMENT(S):

- CHEMISTRY/MICROBIOLOGY  
 PHARMACOLOGY/TOXICOLOGY  
 CLINICAL

IND SAFETY REPORT(S):

- INITIAL WRITTEN REPORT  
 FOLLOW-UP TO A WRITTEN REPORT

RESPONSE TO FDA REQUEST FOR INFORMATION

ANNUAL REPORT

GENERAL CORRESPONDENCE

REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

OTHER Sponsor Comments to FDA Minutes  
(Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

TREATMENT IND 21 CFR 312.35(b)  TREATMENT PROTOCOL 21 CFR 312.35(a)  CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP

DDR RECEIPT STAMP

DIVISION ASSIGNMENT:

IND NUMBER ASSIGNED:

12.

**CONTENTS OF APPLICATION**

This application contains the following items: (Check all that apply)

1. Form FDA 1571 [21 CFR 312.23(a)(1)]
2. Table of Contents [21 CFR 312.23(a)(2)]
3. Introductory statement [21 CFR 312.23(a)(3)]
4. General Investigational plan [21 CFR 312.23(a)(3)]
5. Investigator's brochure [21 CFR 312.23(a)(5)]
6. Protocol(s) [21 CFR 312.23(a)(6)]
- a. Study protocol(s) [21 CFR 312.23(a)(6)]
- b. Investigator data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- c. Facilities data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
- d. Institutional Review Board data [21 CFR 312.23(a)(6)(iii)(b)] or completed Form(s) FDA 1572
7. Chemistry, manufacturing, and control data [21 CFR 312.23(a)(7)]
- Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]
8. Pharmacology and toxicology data [21 CFR 312.23(a)(8)]
9. Previous human experience [21 CFR 312.23(a)(9)]
10. Additional information [21 CFR 312.23(a)(10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION?  YES  NOIF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION?  YES  NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Mila Etropolski, MD, Senior Director, Clinical Team Leader (Chronic Program)  
Johnson & Johnson Pharmaceutical Research and Development, L.L.C

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

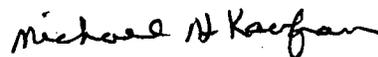
David Upmalis, MD Senior Director, Clinical Team Leader (Acute Program)  
Mila Etropolski, MD, Senior Director, Clinical Team Leader (Chronic Program)  
Johnson & Johnson Pharmaceutical Research & Development, L.L.C

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Michael H. Kaufman  
Director, Regulatory Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18. ADDRESS (Number, Street, City, State and Zip Code)

920 Route 202  
Raritan, NJ 08869

19. TELEPHONE NUMBER (Include Area Code)

908-704-4756

20. DATE

OCT 07 2008

**(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)**

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Amundson Road  
Beltsville, MD 20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

### Supplement to Form FDA 1571 Item 13

Under a license agreement with Grünenthal GmbH, Aachen, Germany, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. has transferred the obligations indicated below for the referenced clinical study to Grünenthal and their US office located at:

Grünenthal USA Inc.  
Crossroads Business Center  
One Pluckemin Way  
Bedminster, NJ 07921

#### Obligations Transferred

Grünenthal GmbH	J&JPRD*	Description	21 CFR Reference
	X	Selection of qualified Investigators	312.53(a)
	X	Control of investigational drug	312.53(b)
	X	Obtaining information from the investigators	312.53(c)
	X	Selection of monitors	312.53(d)
	X	Provide Investigators with the information needed to conduct the investigation properly	312.55(a)
	X	Ensure all participating Investigators in this trial are promptly informed of significant new adverse effects or risks with respect to the drug	312.55(b)
	X	Ensure proper monitoring of the investigation	312.56(a)(b)
X	X	Review of safety information: Review of all information relevant to the safety of the drug obtained or otherwise received from any source	312.32(b)
X	X	Review and evaluate the evidence relating to safety and efficacy of the drug as it is obtained from the investigator (with the exception of reporting to FDA regarding information relevant to the safety of the drug and the annual report as defined below)	312.56(c)
	X	Reporting to FDA regarding information relevant to the safety of the drug	312.56(c) 312.32
	X	IND safety reports and follow-ups	312.32(c)(d)
	X	Submission of annual reports on the progress of the investigation	312.33 312.56(c)
X	X	Discontinue investigations that present an unreasonable and significant risk to subjects	312.56(d)
	X	Maintain adequate records for drug disposition	312.57(a)
	X	Maintain complete and accurate records showing financial interest of investigators participating in the investigation	312.57(b)
	X	Retain records and reports	312.57(c)
	X	Retain reserve samples used in bioequivalence or bioavailability studies	312.57(d)
	X	Disposition of unused investigational drug supply	312.59

\* J&JPRD or Affiliate



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 61,345

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
920 Route 202  
Raritan, NJ 08869

Attention: Michael Kaufman  
Director, Regulatory Affairs

Dear Mr. Kaufman:

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

We also refer to the Type C meeting between representatives of your firm and the FDA on September 5, 2008. The purpose of the meeting was to discuss your plans for development of a novel and effective Tamper Resistant formulation (TRF) of the tapentadol Extended-Release (ER) oral tablets.

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

If you have any questions, call me at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Matthew W. Sullivan  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**SPONSOR MEETING MINUTES**

**MEETING DATE:** September 5, 2008

**TIME:** 12:00 noon to 1:00 pm

**LOCATION:** FDA White Oak Campus  
Silver Spring, MD

**APPLICATION:** IND 61,345

**STATUS OF APPLICATIONS:** Active

**PRODUCT:** Tapentadol HCl

**INDICATIONS:** Moderate to severe pain

**SPONSOR:** Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

**TYPE OF MEETING:** Type C, Guidance

**MEETING CHAIR:** Sharon Hertz, M.D., Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Matthew Sullivan, M.S., Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Bob A. Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Ellen Fields, M.D., MPH	Medical Team Leader, DAARP
Nick Olmos-Lau, M.D.	Medical Officer, DAARP
David Lee, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Lori Love, M.D., Ph.D.	Controlled Substance Staff (CSS)
Craig Bertha, Ph.D.	Chemistry Reviewer, Office of New Drug Quality Assurance
Patrick Marroum, Ph.D.	Expert Office of New Drug Quality assurance
Margarita Tossa, M.S.	Regulatory Project Manager, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager, DAARP
<b>Industry Attendees</b>	<b>Title</b>
<b>Johnson &amp; Johnson Pharmaceutical Research &amp; Development, L.L.C.</b>	
James Buckley	Associate Director, Global Regulatory Affairs, CMC
Mila Etropolski, M.D.	Senior Director, Clinical Leader
Anne Faure	Senior Scientist, Pharmaceutical Product Development

Tania Hillmer	Manager, Global Regulatory Affairs
Michael Kaufman	Director, Global Regulatory Affairs
Pamela Povey, Ph.D.	Director, Global Regulatory Leader
Christine Rauschkolb, M.D., Ph.D.	Vice President, Compound Development Team Leader
Hans Smit, Ph.D.	Associate Director, Clinical Pharmacology
Nancy Van Osselaer	Director, Clinical Pharmacology
Yinka Williams, Ph.D.	Senior Director, Chemical & Pharmaceutical Development
Linda Carter	Sr. Director, Regulatory Affairs, J&J FDA Liaison Office
<b>Grünenthal GmbH</b>	
Silvia Dickhut	International Project Leader
Johannes Bartholomäus, Ph.D.	Head of Pharmaceutical Development
Claudia Lange, M.D.	International Clinical Project Leader
Tom Huijbers	Senior Manager, Regulatory Affairs
Keith Ryan	Manager, Regulatory Affairs USA
Silke Jung, Ph.D.	Head Regulatory Affairs Development
Stefan Buller	Advisor, Clinical Pharmacology

Background:

The Sponsor submitted a meeting package on July 21, 2008, in support of the September 5, 2008, meeting to discuss their plans for further development of a Tamper Resistant Formulation (TRF) of the tapentadol extended-release (ER) oral tablets. The Division provided written responses to the questions in the meeting package on September 4, 2008.

The questions are presented below in *italicized* text in the order in which they were addressed at the meeting. The Division's responses are **bolded**, and the discussion is presented in normal text.

**Chemistry, Manufacturing, and Controls (CMC)**

*Question 1. Does the Agency agree with the following proposals related to TRF drug product stability?*

- 1. The Sponsor will provide 9-months of drug product registration stability data in the New Drug Application (NDA) submission on the 50-and 250-mg strengths and 6-months of drug product registration stability data on the 100, 150, and 200 mg strengths.*
- 2. The Sponsor will provide an amendment no later than 7-months into the NDA review cycle that will include 12-month stability data for each of the tablet strengths.*
- 3. The 12-month stability data will be used as the primary basis to assess the NDA shelf-life proposal.*

**FDA Response:**

**As per the GRMP guidance, we expect applications to be complete at the time of receipt. Additionally, we encourage you to submit at least the minimum amount of data recommended by ICH Q1A at the time of submission for all strengths. Regardless, the expiry will be based on the data that is evaluated during the review cycle.**

**While every effort will be made to review amendments submitted during the review cycle, depending on the timeliness of submission, extent of data, and available resources, we cannot guarantee that all amendments will be reviewed in the first cycle.**

**Stability data should also be obtained at the site intended for commercial manufacture, in addition to the data from the registration site where the clinical and primary stability batches are made. It is not necessarily the case that a demonstration of comparability of BE (proposed with an IVIVC strategy) between product from the two sites guarantees comparable stability profiles. For extended-release solid oral drug products, assuming there is sufficient primary stability data for product from the registration site, it is recommended that the original NDA submission contain 3 months of accelerated and long-term stability data for 3 batches manufactured at the intended commercial site.**

**Bracketing of the intermediate strengths, if necessary, should be justified as outlined in ICH Q1D.**

**Additional CMC Comment:**

**Provide a list of all manufacturing facilities, in alphabetical order, a statement about their cGMP status and whether they are ready for inspections. For all foreign sites, provide a contact name with telephone number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**

**Discussion:**

The Sponsor requested clarification regarding the submission of stability data. The Division replied that site-specific stability would be acceptable, but that the expiry would be based on the data reviewed. The Division further noted that reviewing stability data amendments to a pending NDA is not always feasible, and that the expiry could be based solely on data available at the time of submission. A complete stability package should be submitted at the time of the original NDA submission.

The Sponsor informed the Division that they did not anticipate the requirement to provide stability data from all manufacturing sites, especially given that their sites are comparable to one another. The Division replied that the *Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* is the governing document, and it requires site-specific data from all manufacturing sites. The Sponsor

inquired if they could provide data on the registration batches with the original NDA, and site-specific information at the 4-month update. The Division replied that without a complete CMC section, including all required stability data, the application may not be considered filable.

The Sponsor reported that they intend to provide stability data on two batches of 50-mg tablets and one batch of 250-mg tablets, and asked if this would be acceptable given that the bracketing proposal will be submitted with the NDA. The Division replied that the bracketing must be consistent with ICH Q1D, and that it should include three batches of each strength. The Sponsor asked if they could submit the bracketing proposal to the IND, prior to the NDA submission, to which the Division replied in the affirmative.

### **Preclinical Toxicology**

*Question 2. Does the Agency agree that no further preclinical testing is needed for the TRF formulation?*

#### **FDA Response:**

**Based on the information provided, no further testing appears necessary at this time. However, any excipients, impurities or degradation products that are novel or exceed the threshold for qualification, may require additional nonclinical support for safety.**

#### Discussion:

There was no additional discussion beyond the information provided in the response.

### **Clinical Pharmacology**

*Question 3. Does the Agency agree that the dose proportionality of tapentadol TRF can be assessed from single-dose studies using a cross-study assessment along with supportive data obtained from previous studies with the extended-release formulation (PR2) on dose linearity and dose proportionality?*

#### **FDA Response:**

**Yes, pending a favorable outcome from the proposed pivotal BE studies (50 and 250 mg). Additionally, you need to request a biowaiver for the intermediate doses.**

#### Discussion:

There was no additional discussion beyond the information provided in the response.

*Question 4. Does the Agency agree that the effect of food on the to-be-marketed (TBM) TRF, and appropriate labeling thereof, can be assessed from a cross study assessment of single-dose data from the relative bioavailability (BA) study of 250 mg TRF vs. PR2 under fed conditions (Study PAI-1024/HP35) and the planned pivotal BE study of 250 mg TRF vs. PR2 under fasting conditions (Study PAI-1033/HP31)?*

**FDA Response:**

**Yes, we agree.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 5. Does the Agency agree that the relative BA study of the highest dose strength, i.e., 250 mg TRF vs. PR2 under fed conditions (Study PAI-1024/HP35) fulfills the recommendation to describe the in vivo performance of to-be-marketed TRF versus PR2 under fed conditions?*

**FDA Response:**

**Yes, we agree.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 6. Reference is made to the IVIVC study results for tapentadol TRF at the highest dose strength:*

- a. Does the Agency agree that the IVIVC at the 250 mg strength was conducted in a manner consistent with the principles in the Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations and demonstrates a Level A correlation?*

**FDA Response:**

**Yes, we agree that the IVIVC was conducted in a manner consistent with the IVIVC guidance. It should be noted that the convolution of the plasma concentration time profile should be done using the mean plasma concentrations and not the individual subjects since the decisions are based on mean dissolution profiles. Individual input functions are not available for each subject and using the same mean input function might not be optimal because one cannot assume that all the subjects will have the same in vivo absorption characteristics. Moreover, when the IVIVC will be applied for SUPAC-type changes the regulatory decisions are going to be based on mean input function as well as mean disposition characteristics. No individual data for each subject will be available to calculate the predictions.**

**Discussion:**

The Sponsor referred the Division to Attachment 2 in the meeting background materials regarding the in vitro/in vivo correlation (IVIVC) study. The Division replied that decisions regarding the applicability of the IVIVC will be made based on mean data. Therefore, the

convolution predictions should be made on the mean profiles and not on data from individual subjects. The Sponsor acknowledged the Division's response.

- b. *Does the Agency agree that the approach of doing an IVIVC study that is being established at the 250 mg dose strength of the TRF formulation is applicable to the to-be-marketed TRF formulation at all dose strengths (50, 100, 150, 200, and 250 mg)?*

**FDA Response:**

**Yes, we agree provided the IVIVC is able to also predict the lower strengths. Prediction errors for the lower strengths should also be evaluated using the IVIVC developed with the highest strength.**

**Discussion:**

The Sponsor inquired as to the nature of the "prediction errors." The Division replied that the predictions errors obtained for the lower strengths should meet the criteria outlined in the IVIVC guidance.

- c. *Does the Agency agree that these IVIVC data will provide sufficient support to waive bioequivalence studies for a site change between the registration batch manufacturing site and the process validation/commercial batch manufacturing site?*

**FDA Response:**

**Yes, we agree.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

- d. *Does the Agency agree that these IVIVC data will provide sufficient support to waive bioequivalence studies for Post-Approval Changes of the TRF when applicable Center for Drug Evaluation and Research (CDER) guidelines (e.g., SUPAC-MR: Modified Release Solid Oral Dosage Forms) indicate that such waivers may be appropriate?*

**FDA Response:**

**Yes, we agree.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 7. The Sponsor will include the following studies to bridge the to-be-marketed TRF formulation to the clinical PR2 formulation:*

- a. Two pivotal bioequivalence (BE) studies (50 mg and 250 mg TRF vs. PR2) under fasted conditions*
- b. Relative BA studies on 50, 100, and 250 mg TRF vs. PR2 under fasted conditions*
- c. Relative BA study on 250 mg TRF vs. PR2 under fed conditions*
- d. IVIVC data on highest dose strength (250 mg) of the to-be-marketed TRF*
- e. Comparative dissolution on each strength of TRF (development) vs. PR2 (clinical) counterpart*
- f. Comparative dissolution on each strength of TRF (commercial site) vs. TRF (development) counterpart*

*Does the Agency agree that the proposed studies will provide sufficient information to bridge the to-be-marketed TRF to the clinical PR2 for all dose strengths (50, 100, 150, 200, and 250 mg)?*

**FDA Response:**

**In the presence of an IVIVC, F2 should not be calculated. Comparability of the dissolution profiles should be based on the predicted plasma concentration profiles and not the F2 similarity factor.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 8. Does the Agency agree that the proposed multiple-dose PK study design is acceptable to document the multiple-dose pharmacokinetics of tapentadol TRF for labeling purposes?*

**FDA Response:**

**Yes, we agree.**

**Discussion:**

There was no additional discussion beyond the information provided in the response.

*Question 9. Does the Agency agree that the proposed study design of the alcohol effect study to investigate possible in vivo dose dumping of tapentadol from the to-be-marketed TRF formulation fulfills the FDA requirements?*

**FDA Response:**

**It seems that you are proposing to test only 40% V/V alcohol concentration based on negative findings in the vitro assessment of the dose dumping potential and that you want to confirm this finding in vivo under worst case scenario. Based on this, your proposal to study only 40% V/V alcohol concentrations seems reasonable. However, it is not clear why you are proposing to test both 100 mg and 250 mg strengths.**

**Discussion:**

The Sponsor noted that they are proposing to test both 100-mg and 250-mg strengths purely for patient safety. They stated that, although they have no reason to suspect that dose dumping will occur, prudence dictates that they start with the 100-mg dose. The 250-mg dose will then be tested if there are no safety issues or unacceptable increases in  $C_{max}$  with the 100-mg dose. The Division concurred with this plan.

**Additional CSS Comment:**

**In Attachment 1: Tamper Resistant Property Studies, you provided a brief summary of proposed studies to evaluate the physicochemical properties of Tapentadol TRF formulation that might deter tampering and misuse. Complete protocols and detailed study results are necessary to evaluate the adequacy of the proposed studies, and whether there is a need for additional data. In general, we recommend you provide the following:**

- 1. Data to assess the effects of biting and chewing on the release of Tapentadol TRF from intact tablets and from tablets presoaked in artificial saliva or water.**
- 2. Data from in vitro studies to assess the amount of Tapentadol TRF release (% label claim) from intact, crushed and ground tablets, exposed to various solvents, variable temperatures (room temperature and at temperatures at or near the boiling point of selected solvents) and agitation. Solvents for consideration include those of various polarities (water, 40 % alcohol, absolute alcohol, methanol, oil, etc) and different pHs.**
- 3. Data on [REDACTED] (b) (4)**

**Discussion:**

The Sponsor inquired about specific recommendations that the Division could provide regarding the tamper resistant aspects of the formulation. The Division replied that they strongly recommend the Sponsor review the May 5, 2008, Advisory Committee meeting minutes, with specific attention paid to the discussion of protocol design and scientific rigor. The Division also

noted that the Sponsor should ensure that the study design is statistically and scientifically adequate.

The Sponsor asked if the Division would accept data generated from in-house testing, rather than from an outside contractor. The Division replied that if the methods of the study are scientifically rigorous, there is no reason why in-house data would not be acceptable. The Division also advised the Sponsor to consult with scientists who have expertise on extractability, and also to consult with drug abusers from the community to provide insight into how these products are abused and misused.

Action Items:

1. The Sponsor will provide stability data as requested by the Division. If the Sponsor desires to bracket the strengths, a proposal will be provided prior to the submission of the NDA.
2. The Sponsor will conduct an alcohol effect study with a 100-mg dose initially, and then a 250-mg dose if no safety issues arise.
3. Physicochemical properties of the TRF formulation will be appropriately evaluated, taking into account the May 5, 2008, Advisory Committee discussion. The Sponsor will ensure that the protocols and study designs are conducted with scientific rigor.

Linked Applications

Sponsor Name

Drug Name

IND 61345

JOHNSON AND  
JOHNSON  
PHARMACEUTICAL  
RESEARCH AND  
DEVELOPMENT LLC

CG5503

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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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MATTHEW W SULLIVAN  
09/30/2008



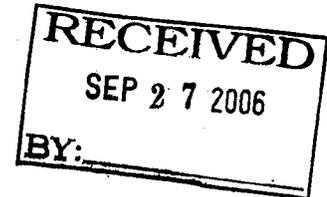
**DEPARTMENT OF HEALTH & HUMAN  
SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 61,345

Johnson & Johnson Pharmaceutical Research & Development, LLC  
1125 Trenton-Harbourton Road; PO Box 200  
Titusville, NJ 08560



Attention: Kathleen F. Dusek, RPh, RAC  
Associate Director, Global Regulatory Affairs

Dear Ms. Duseck:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tapentadol Hydrochloride (CG5503/R331333).

We also refer to the meeting between representatives of your firm and FDA on August 24, 2006. The purpose of the meeting was to discuss your Phase 3 development of Tapentadol Hydrochloride (CG5503/R331333).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1175.

Sincerely,

*{See appended electronic signature page}*

Lisa Basham, MS  
Regulatory Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

### Meeting Minutes

**MEETING DATE:** August 24, 2006

**TIME:** 1:30 PM

**LOCATION:** White Oak; Building 22; Room 1313

**APPLICATION:** IND 61,345

**STATUS OF APPLICATION:** Active

**PRODUCT:** Tapentadol Hydrochloride (CG5503/R331333)

**INDICATION:** moderate-to-severe pain

**SPONSOR:** Johnson & Johnson

**TYPE OF MEETING:** End-of-Phase 2

**MEETING CHAIR:** Sharon Hertz, MD, Division of Anesthesia,  
Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Lisa Basham, Regulatory Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Robert Meyer, MD	Director, Office of Drug Evaluation II (ODE II)
Curtis Rosebraugh, MD	Deputy Director, ODE II
Bob Rappaport, MD	Division Director
Sharon Hertz, MD	Deputy Division Director
Tom Permutt, PhD	Acting Director, Division of Biometrics 2
Mwango Kashoki, MD	Clinical Team Leader
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Dionne Price, PhD	Statistics Team Leader
Adam Wasserman, PhD	Supervisory Pharmacologist
Robert Shibuya, MD	Clinical Reviewer
Joan Buenconsejo, PhD	Statistics Reviewer
David Lee, PhD	Clinical Pharmacology Reviewer
Lisa Basham, MS	Regulatory Project Manager
<b>Industry Attendees</b>	<b>Title</b>
<i>J&amp;JPRD</i>	
Kathleen Basmadian, PhD	Senior Director, Regulatory Affairs
Ravi Desiraju, PhD	VP, Compound Development Team Leader
Kathleen Dusek, RPh, RAC	Associate Director, Regulatory Affairs
Mila Etropolski, MD	Director, Medical Leader
Peggy Ferrone	Manager, Regulatory Affairs
Juergen Haeussler, MD	VP, Therapeutic Area Head Pain
David Hilfiker, MS	Associate Director, Regulatory Affairs, J&J FDA Liaison Office
Bernhard Mangold, MD, PhD	Director, Clinical Pharmacology
Akiko Okamoto, ScD	Assistant Director, Clinical Biostatistics
Pamela Povey, PhD	Global Regulatory Affairs Leader
Christine Rauschkolb, MD, PhD	Senior Director, Clinical Team Leader
Barry Schwab, PhD	Executive Director, Clinical Biostatistics
<i>Grunenthal</i>	

Burkhard Daldrup, PhD	Head of Corporate Regulatory and Safety Affairs
Bettina Doepner, PhD	Senior Regulatory Affairs Manager
Claudia Lange, MD	International Clinical Project Leader
Anton Hoos, MD	Head of Development
Achim Steup, MSc	Biostatistical Expert (Grunenthal USA, Inc.)
Horst Weber, MD, PhD	Global Head Development Analgesics
Gernot Wolfram, MD	Clinical Expert, Therapeutic Area Analgesics

**Background:** The sponsor submitted a request for an End-of-Phase 2 meeting, dated April 21, 2006. This meeting was scheduled for August 24, 2006. Prior to the meeting, the Agency prepared responses to the questions posed in the July 14, 2006, meeting package. These responses were forwarded to the sponsor on August 23, 2006. Prior to the meeting, the sponsor requested that discussion focus on questions 4b, 5, 6, 7a, 7b, 8, 9, 11, 12, 13, 15, and 16. Furthermore, they expressed their desire to discuss these responses in the following order: 9, 11, 12, 7a, 7b, 8, 4b, 5, 6, 15, 13, and 16.

**Note:** The questions included in the meeting package are shown below in italicized text. Agency responses/comments/questions, forwarded to the sponsor prior to the meeting, are shown below in bolded text. Discussion during the meeting is presented in normal text.

Prior to discussing the Agency responses, the sponsor offered the following opening remarks. They stated that they have been struggling with how to formally demonstrate efficacy for their drug in a chronic pain clinical study that incorporates all of the Division's requirements of a non-enriched design, fixed dosing, and baseline observation carried forward. They continued that they have observed trials that combine one or two of these features result in a demonstration of efficacy, but no trials that combine all three features. They expressed their interest in discussing this further with the Division in the context of the responses provided.

*Question 9*

*Is the dose range proposed as 100 to 250 mg CG5503 ER base b.i.d. with 50 mg used only for titration purposes, acceptable to the Division for the 4-week and 12-week key efficacy trials?*

**Agency Response:**

- **The highest proposed dose (250mg BID) exceeds the exposures studied in the completed tQT study (HP5503/10). The proposed tQT study (HP5503/18) may or may not achieve exposures comparable to those predicted for 250 mg of the ER formulation dosed BID. In order to support maximum doses of 250mg BID for the efficacy trials, at a minimum, study HP5503/18 will have to be completed and analyzed and the pharmacokinetic data compared to the steady-state exposures modeled for 250 mg CG5503-ER dosed BID.**

- **Assuming that the cardiac safety issues are adequately addressed, the proposed dose range appears reasonable for the OA and CLBP studies given the exclusions in the protocol. These exclusions will be included in the labeling.**

The sponsor stated that they have data showing exposures greater than 250 mg that have shown no QT effect. The dose-escalation study (HP5503/13) examined multiple doses of 125 mg IR q6h and multiple doses of 150 mg IR q6h. ECG recordings were done at baseline and at steady state on Day 2. Dr. Hertz expressed concern regarding a lack of knowledge about when QT signals may be occurring versus when the measurements were taken in prior studies. The sponsor reiterated that they are comfortable that the doses in the Phase 3 studies have been adequately tested for QT effect and also that the careful titration in those studies should minimize risk even further. The sponsor had planned to perform a thorough QT study in parallel with the Phase 3 studies. Dr. Hertz stated that running the thorough QT study in parallel with the Phase 3 studies is acceptable. The sponsor should submit the report for Study HP5503/13 for review prior to initiating dosing up to 250 mg BID in Phase 3. The sponsor should double check that the C<sub>max</sub> for an oral dose of 250 mg BID is no higher than for a dose of 40 mg IV.

*Question 11*

*The Sponsor plans to perform the Phase 3 trials without collecting information when study drug was taken in relation to time of food intake and composition of food. Does the Division agree with this proposal?*

**Agency Response:**

**No. Study HP 5503/08 showed a marked (60.8%) food effect on the C<sub>max</sub> with the ER formulation and adverse event data show dose-dependent increases in common AEs (nausea, dizziness, vomiting). Therefore, we strongly recommend that you systematically collect the conditions of administering the drug with respect to whether the patient is in the fed or fasted state, in order to be able to evaluate the effect on the adverse event rate. Without adequate evidence of safety in the fed state, and with regard to existing information on dose-related AEs, it may be necessary to label the product for dosing on an empty stomach.**

The sponsor clarified that an earlier formulation of drug had a 60% food effect, but that the later formulation (ER 2) showed a 28% effect on C<sub>max</sub> and an 11% effect on AUC when 300 mg was administered with a high fat meal. They expect similar results in the proposed Phase 3 study, in which 250 mg will be administered (Formulation ER2). In addition, given the approximate 2-fold accumulation at steady state, they would expect the food effect to disappear in the overall variability of the pharmacokinetic data. It was agreed that conducting Phase 3 studies without respect to food intake is acceptable. The sponsor agreed to combine the food effect data from the old and new formulations (ER1 and ER2, respectively) into one table and submit to the Agency for review prior to conducting the Phase 3 efficacy studies.

*Question 12*

*Based on this background information and available data, the Sponsor plans to conduct a standard safety ECG evaluation in Phase 3 trials. Does the Division concur with this proposal?*

**Agency Response:** Given the current available data, the proposed ECG evaluations in Phase 3 are acceptable. If however, the planned tQT study results in a "signal," you may need to amend the Phase 3 program.

This was discussed under question 9 and no further discussion is necessary.

*Question 7a*

*Does the Agency agree with the proposed study design with a 4-week withdrawal phase in a cancer pain population?*

**Agency Response:**

**An abrupt withdrawal of an opioid is not acceptable in a study of opioid tolerant patients. Even a low incidence of overt withdrawal exposes patients to unnecessary adverse events. The study drug and morphine comparator must be slowly weaned at any point the drug is to be discontinued so that there is no evidence of withdrawal. It is important to note that subtle signs of opioid withdrawal can include pain. There may not be any method for distinguishing return of pain and withdrawal-induced pain in this setting.**

The sponsor expressed their understanding that pain as a symptom of opioid withdrawal can confound the efficacy measure and their agreement to conduct a stepwise taper of the opioid over several days.

*Question 7b*

*Does the Agency agree that by allowing the intake of rescue medication as required and implementation of analytic measures, e.g., endpoint definition, COWS, and SOWS, confounding with withdrawal symptoms will be adequately avoided?*

**Agency Response:**

**No. This is theoretical. A taper would be more appropriate to avoid the confound previously described.**

The sponsor inquired whether the Division would recommend using COWS and SOWS even with a tapering scheme. Dr. Hertz responded that this information would be very informative for this new molecular entity. The sponsor noted that their use of SOWS would be limited to English speaking countries and that question 16, relating to IV drug use, would be eliminated. The Division agreed with this proposal.

*Question 8*

*Is this primary endpoint for the cancer pain study acceptable to the Agency?*

**Agency Response:**

- **For the cancer pain study, the definition of responder is not acceptable as proposed. In particular, the criterion of PI <5 is problematic as the PI entry criterion is  $\geq 5$  so that even a change of 1 point on the scale would meet this criterion. You may want to consider a percent change (e.g. 30%) or an absolute change in score (e.g. 2 pts)**
- **The definition of responder should encompass the entire 28 days of the maintenance phase, not the last 25 days as proposed.**

The sponsor explained that patients entering the double-blind period have been optimally titrated and are allowed rescue medication. Therefore, patients will either maintain their pain level or worsen. In other words, the definition of a responder is a patient that maintains the benefit of the drug. Patients who worsen are non-responders. Additionally, non-responder criteria are as follows: patients who do not complete 28 days of treatment, or increase pain intensity to a VRS score of greater than or equal to 5 on average, or use more than 2 doses of rescue medication per day on average. The sponsor has used this method of study when evaluating another compound, where the responder rate was 75% for study drug versus 50% for placebo. They added that intake of rescue medication was the driving force behind the results. Dr. Hertz expressed an interest in seeing this data along with the sensitivity analysis, the levels of pain intensity, and the use of rescue medication. The Division will attempt to review this and include comment as a post-meeting note regarding the acceptability of the design for the pivotal cancer study.

POST MEETING NOTE: The data regarding the other compound was provided via email on September 14, 2006. The Division was unable to evaluate these data prior to issuing the minutes of the meeting, but will attempt to evaluate the submission and provide feedback to the sponsor in a timely manner.

Regarding the second bullet, the sponsor stated that, due to operational issues, a patient may come into the clinic one day more or less than the pre-defined date. Dr. Hertz responded that this is acceptable as long as the variation is due to operational reasons only.

Dr. Hertz stated that the cancer study may be acceptable as a pivotal study if the sponsor and the Division can agree on the design.

*Question 4b*

*Does the Division agree with the proposed controlled dose adjustment design for CG5503 in the 12-week maintenance phase?*

**Agency Response:**

- **No. As discussed in the December 2005 EOP2 meeting, because CG5503 is a New Molecular Entity with a poorly defined upper dosing range, the maintenance phase of the OA and CLBP trials must use a fixed dose.**
- **Using a flexible scheme in the titration phase is acceptable, however, patients may cluster in a small range of doses. This may limit the efficacy data to a narrow dosing range which would be reflected in the labeling.**

The sponsor expressed their understanding of the Division's concern regarding a poorly defined upper dosing range. They added, however, that they are not sure that they can deliver a technically successful study with fixed dosing. Dr. Hertz stated that, in general, there are different items that must be obtained in order to understand this new molecular entity, including getting a clear understanding of dosing (including dose-response and dose range) such that we can make recommendations in the label. If a study designed to obtain this dosing information is unlikely to result in a successful trial then the sponsor should consider how this information may otherwise be obtained. The sponsor stated that they envision a comprehensive program that includes studies that employ combinations of the requirements expressed previously by the division (i.e., randomized-withdrawal, enriched with fixed dosing, and flexible dosing).

Dr. Rappaport stated that, since this is a New Molecular Entity, two trials are needed, only one of which may study an enriched population. Information regarding dosing and the ceiling effect are needed. Dr. Hertz stated that there may be other ways to obtain the necessary information, i.e., all information may not need to be obtained in one trial. Dr. Rappaport inquired whether the sponsor has conducted a Phase 2 fixed-dose study. They responded affirmatively, but noted that this 29-day trial did not explore doses above 200 mg. The sponsor suggested that by providing patients with the option of titrating upward, information on dosing and the ceiling effect may be obtained. Dr. Rappaport responded that a study of this design would require rigorous data gathering to obtain the information needed. In a study with variable dosing, he added, it is difficult to fully assess the relationship between dose and adverse events. Dr. Hertz stated that a small number of patients at the highest dose may not provide enough support for that dose. She added that, for the mid-range doses, the numbers are not as problematic. The high- and low-dose information, however, may be difficult to obtain. The sponsor expressed their understanding that, if a low percentage of patients end up on the high dose, that dose would not be recommended in the labeling. Dr. Hertz suggested the sponsor lay out how they foresee where the required information would be obtained in their comprehensive program and submit it to the Division. She added that the Division will look at the submission, but cannot guarantee a turn-around timeframe. The sponsor inquired whether a fixed-dose study with a less conservative imputation method would answer our questions. Dr. Rappaport stated that it is unlikely that this type of study would answer the questions, but that it may.

The sponsor stated that they plan to submit the acute application first and inquired at what point the moiety is no longer considered an NME. Dr. Rappaport responded that the moiety is no longer an NME after the first application for that moiety has been approved. Dr. Hertz noted that safety data from chronic studies can be used to support

the application for the acute indication, but that safety and efficacy from the acute application has minimal utility in supporting the chronic indication.

The sponsor summarized their understanding that dose-response and dose-range are important elements of the drug development program for this NME. They plan to put together a program plan describing how they foresee the necessary information being obtained from different trial types. They will attempt to devise a portfolio of studies that address all concerns, but where all of the Divisions recommendations regarding trial design may not be met in all trials. Dr. Hertz reiterated that this information is critical, not just because this compound is not a pure opioid, but because this is also a novel compound.

*Question 5*

*Does the Division concur with the proposed methods of imputation for statistical analyses?*

**Agency Response:**

- **For the OA and CLBP studies, last observation carried forward (LOCF) is not considered appropriate as the primary method of handling missing data. Patients who drop out for adverse events may have good pain scores carried forward even though they were not successfully treated. Instead, we recommend that the alternate imputation method you proposed (baseline carried forward analysis) be applied as the primary method of handling missing data.**
- **For the cancer study, because of the proposed endpoint (response rate), imputation of scores should only be necessary for missing data between recorded PI scores. Interpolation or a similar method of imputation will be acceptable. For patients failing to record pain scores on Day 28, those patients should be considered non-responders. LOCF is not an acceptable imputation method for an analysis of a comparison of means in an analgesic trial.**

Dr. Hertz explained further that drop-outs in these trials are generally based on treatment assignment and are not random. Dropouts due to adverse events are more common in the active treatment arm while dropouts due to lack of efficacy are more common in the placebo arm. Good scores cannot be given to patients who drop out due to adverse events and therefore cannot tolerate the drug.

Dr. Rappaport reiterated the shortcomings of the LOCF imputation approach. He continued that the sponsor may analyze the data using any imputation method they choose, but that the Division would most likely reanalyze the data using BOCF.

*Question 6*

*The primary efficacy endpoint for the pivotal Phase 3 studies for non-malignant pain is the change from baseline (average pain intensity during the last 3 days prior to randomization) of the average pain intensity over the 12 weeks maintenance period, using daily measurements on an 11-point numeric rating scale (NRS). Is this primary endpoint acceptable to the Division?*

**Agency Response:**

**No. The primary endpoint should compare the pain intensity at baseline versus the pain intensity at week 12. The proposed average pain intensity over 12 weeks would be important as a secondary endpoint.**

The sponsor stated that they wish to use the average pain intensity up to week twelve as the primary measure. Dr. Permutt responded that the primary measure must be at week twelve and drop-outs must be assigned a bad score. The sponsor expressed their desire to analyze pain scores over time. Dr. Permutt stated that the sponsor can collect useful information over the twelve-week period, but that the efficacy measure should be a comparison of baseline to week twelve because efficacy over a shorter period early in the trial could result in a positive outcome, but would not be sufficient to define clinically appropriate efficacy. Therefore, he continued, evaluation of efficacy at the end of the trial is required. The twelve-week time point is actually a surrogate for months and years. In addition to looking at the end-of-treatment analysis to evaluate durability of effect, we will also look at what happened while getting there, to evaluate the effect over time. Dr. Hertz added that the average of the twelfth week is acceptable as the end-of-treatment time point.

The sponsor stated that there is some evidence that opioid use may change some people for good, i.e., their pain levels may improve permanently. Some require use for 1 week, some for 1 year, some for 10 years. They plan to ask the patient if they feel their pain has improved after the treatment period through a follow-up assessment. Dr. Hertz suggested that the issue of tolerance may also be explored using this follow-up method. If the patients have been tolerating adverse events because their pain has been controlled, but the pain-relief is diminishing, this is an indication of tolerance. This information would be very informative to capture.

The sponsor also plans to explore the reasons for drop-outs in this follow-up procedure. Patients will be followed through approximately 14 weeks, whether they drop out of the study or not.

The sponsor summarized that treatment will be evaluated at week twelve (average of week twelve acceptable). The sponsor will also evaluate the patient global improvement of change and follow-up through week 14 for all patients, including drop-outs.

*Question 15*

*Will positive results from any combination of two of the above study designs, 4-week cancer study utilizing randomized withdrawal and/or 12-week OA or LBP study utilizing flexible titration to optimal dose and controlled dose adjustments throughout maintenance be acceptable to support approval of an indication for the treatment of moderate to severe chronic pain?*

**Agency Responses:**

**The cancer pain study, as proposed, is not appropriate to provide substantial support for a finding of efficacy. The OA and CLBP trials require amendments for the primary outcome and analysis plan. As both of these studies are designed with flexible dosing, they may not provide adequate data to support a dosing range if patients self titrate to a small range of doses.**

Dr. Hertz noted that the Division will review the sponsor's comprehensive "portfolio" of planned studies to address this issue further.

(b) (4)



*Question 16*

*Will the submission of an additional safety update before 7-months expiration of the review clock be acceptable to the Division without incurring an extension of the 10-month review clock?*

**Agency Responses:**

**The CFR describes the requirement to submit one safety update, 120 days following the initial submission. Any new data received in the last 3 months of the review cycle may not be reviewed during the first review cycle.**

Dr. Hertz reiterated the Division response that, if important information is submitted seven months into the review cycle, it may not be reviewed during that cycle. She suggested that the sponsor delay submission of the NDA such that all safety information is submitted with the 120-day safety update. If the sponsor opts to submit this information later, and a signal has been identified, we would have to determine whether this submission is a major amendment, which would extend the clock. Dr. Meyer noted that the Division may request a safety update prior to completion of their review, but unless there is a significant safety signal, a submission resulting from this Agency request would not extend the clock.

*Additional Regulatory Items:*

*RiskMAP*

*The sponsor has proposed development of a risk minimization action plan in consultation with the division and the Controlled Substances Staff.*

*Peds*

*The sponsor proposes to request a waiver for PK and chronic pain studies in pediatric patients* (b) (4)

**Agency response:**

**A request for waiver for pediatric studies must be supported by a sound clinical rationale. Given that chronic pain can extend to very young children, you may have to study this population unless a rationale for why it would not be feasible can be provided.**

The sponsor asked for guidance on the lowest age group to investigate for chronic pain conditions. Dr. Hertz responded that PREA addresses the moiety, and that they may need to develop a new formulation for use in very young children. The sponsor's rationale for

a waiver, she continued, would have to address the lack of need in the younger age groups to merit the waiver.

Dr. Hertz stated that this compound will be assessed for scheduling and suggested that the sponsor begin thinking about a Risk Management Plan. She continued that the Agency now requires that a plan be in finalized form at NDA submission. The Division will evaluate such a plan a priori in preparation for the NDA submission. Dr. Meyer clarified that the plan does not have to be fully negotiated at filing, but that it must be fleshed out and ready for meaningful review.

The following responses were not discussed during the meeting.

*QUALITY*

*Question 1*

*Does the Agency agree with the designation of [REDACTED] (b) (4) for the synthesis of tapentadol HCl active pharmaceutical ingredient?*

**Agency Response:**

**In order to qualify [REDACTED] (b) (4) the following information needs to be provided:**

- **Manufacturing/synthesis details [REDACTED] (b) (4)**
- **Tests data confirming that none of the impurities contain a potential structural alert for genotoxicity [REDACTED] (b) (4)**
- **Data showing that impurities of the starting material are not carried over to the final drug substance (purging studies)**
- **Long term stability studies showing that the [REDACTED] (b) (4) remains stable during the proposed storage time (your data, up to 77 days at refrigerated conditions, indicated that the starting material is degrading).**
- **Acceptance criteria for [REDACTED] (b) (4)**
- **In addition to the GC method (e.g. HPLC), you need to develop an additional method for the detection and quantitation of the impurities [REDACTED] (b) (4)**

NO DISCUSSION NECESSARY.

*Phase I Program*

*Question 2a*

*Does the Division agree that the performed Phase 1 studies (using both immediate release (IR) and extended-release (ER) formulations) describe the pharmacokinetics of CG5503 sufficiently to support the Phase 3 program for chronic pain?*

**Agency Response:**

**Yes. The pharmacokinetic studies conducted to date support a Phase 3 program for CG5503-ER.**

NO DISCUSSION NECESSARY.

*Question 2b*

*Does the Division agree that the planned Phase 1 studies will assess the pharmacokinetics of CG5503 sufficiently in order to support the NDA submission for chronic pain?*

**Agency Response:**

**Yes. The completed and planned pharmacokinetic studies for CG5503-ER appear appropriate to support an NDA submission.**

NO DISCUSSION NECESSARY.

*Phase 2 Program*

*Question 3*

*Does the Division concur that the combined Phase 1 and 2 studies as outlined in the Clinical Overview, Appendix 3, Table 2 and Table 4, sufficiently describe the pharmacokinetics, pharmacodynamics, safety and tolerability of extended-release (ER) CG5503 to support the Phase 3 program?*

**Agency Response: Yes**

NO DISCUSSION NECESSARY.

*Phase 3 Program*

*Question 4a*

*Does the Division agree with using the proposed titration design and a dose of 50 mg CG5503 base as a starting titration dose?*

**Agency Response: Yes**

NO DISCUSSION NECESSARY.

*Question 10*

*Does the Division agree that the population studied will be sufficiently representative to support an indication for moderate to severe chronic pain?*

**Agency Response: Yes**

NO DISCUSSION NECESSARY.

*Question 14*

*Does the Division agree that the proposed safety population at the proposed therapeutic dose range for CG5503 will provide sufficient safety data for registration purposes?*

**Agency Responses:**

**Yes as long as there is adequate exposure to the highest proposed doses. This will be important because of the one reported seizure in Phase 1 and because of similarities in pharmacology to tramadol. The safety database should include a substantial number of patients treated at the highest labeled dose.**

NO DISCUSSION NECESSARY.

*Question 15*

*Will positive results from any combination of two of the above study designs, 4-week cancer study utilizing randomized withdrawal and/or 12-week OA or LBP study utilizing flexible titration to optimal dose and controlled dose adjustments throughout maintenance be acceptable to support approval of an indication for the treatment of moderate to severe chronic pain?*

**Agency Responses:**

**The cancer pain study, as proposed, is not appropriate to provide substantial support for a finding of efficacy. The OA and CLBP trials require amendments for the primary outcome and analysis plan. As both of these studies are designed with flexible dosing, they may not provide adequate data to support a dosing range if patients self titrate to a small range of doses.**

**KEY DISCUSSION POINTS:**

1. **The sponsor will identify the location of data from study HP5503-13 or resubmit the study report for Division review. The sponsor will submit these data for review prior to initiating the Phase 3 trials at a maximum dose of 250 mg BID.**
2. **It is acceptable to perform the Phase 3 study and the tQT study in parallel.**
3. **Food intake does not need to be controlled in the Phase 3 trials, however, the sponsor will submit the information regarding food-effect for the ER1 and ER2 formulations for review by the Division prior to initiating the Phase 3 trial.**
4. **The cancer pain study (randomized withdrawal) is acceptable as a pivotal trial pending clarification of combined responder criterion. The Sponsor accepted the addition of a step-wise taper over several days upon randomized withdrawal.**
5. **FDA explained the need for being able to assess dose-response and dose range (particularly at the highest dose) when reviewing the NDA. FDA considers a fixed-dose trial with a conservative imputation method and a 12-week endpoint analysis to be a study design that should allow for such an assessment. It is possible, however, that the necessary information could be gathered through a combination of studies rather than through studies incorporating all features. The Division offered to review a proposal that provides a detailed explanation of how these criteria may be met through a comprehensive program.**
6. **The sponsor will utilize COWS and SOWS to evaluate withdrawal effect.**
7. **The sponsor will explore the possibility of sharing trial design data with the Division from a different compound that utilizes measures of pain intensity and rescue.**
8. **The sponsor will assess the patient global assessment of change at week 14. All patients will be followed, including drop-outs.**
9. **Comparator AEs will not be permitted in the label, as it implies a claim. Comparative statements can only be included in the label if studied in a controlled fashion. Additional studies with specific designs (e.g., cross-over) with replication, validation and appropriate statistical evaluation would be required to make comparative claims.**
10. **The sponsor must provide a clinical rationale for requesting a waiver from studying pediatric patients [REDACTED] (b) (4)**
11. **The sponsor will begin considering a RiskMAP for this compound, which will be evaluated for scheduling.**

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Lisa Basham-Cruz  
9/22/2006 09:37:00 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 61,345

Grunenthal USA Inc.  
Crossroads Business Center  
One Pluckemin Way  
Bedminster, NJ 07921

Attention: Richard A. Paul  
COO/Executive Vice President; Development Regulatory Affairs

Dear Mr. Paul:

Please refer to the meeting between representatives of your firm and FDA on November 13, 2003. The purpose of the meeting was to discuss your clinical development plan for CG5503.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

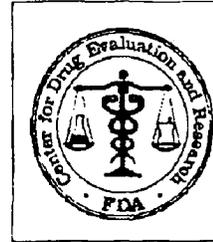
If you have any questions, call me at 301-827-7420.

Sincerely,

*{See appended electronic signature page}*

Lisa E. Basham-Cruz  
Regulatory Project Manager  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure



**MEETING MINUTES**

**Meeting Date:** November 13, 2003

**Location:** Parklawn Building, Potomac Conference Room

**IND; Name:** IND 61,345; CG5503

**Sponsor:** Grunenthal USA Inc.

**Type of Meeting:** Type C Industry Meeting

**Meeting Chair:** Sharon Hertz, M.D.  
Division of Anesthetics, Critical Care, and Addiction Drug Products

**Attendees:**

Sponsor	Title
<b>(Grunenthal, GmbH)</b>	
Dr. Bettina Doepner	Global Regulatory Affairs
Dr. Christoph Hallmann	International Clinical Project Manager
Ms. Regina Kleinart	International Project Management
Dr. Ferdi Rombout	PK/PD Modeling & Simulation Scientist
Dr. Horst Weber	Project Leader
Dr. Burkhard Daldrop	Head of Global Regulatory Affairs
Mr. Achim Steup	Project Statistician (Grunenthal USA, Inc.)
Dr. Richard Paul	Chief Operating Officer/Executive VP, Reg. Affairs
<b>(J&amp;JPRD)</b>	
Dr. Debra Barrett	Compound Development Team Leader
Ms. Peggy Ferrone	Manager, Regulatory Affairs
Dr. Juergen Haeussler	Sr. Director, Global Clinical Franchise Leader, Pain
Dr. Brigitte Kuperwasser	Associate Director, Clinical Affairs
Dr. Elizabeth Mutisya	Senior Director, Clinical Affairs
Ms. Toni-Marie Nearing-Crowley	Associate Director, Regulatory Affairs
Dr. Scott Reines	VP and Therapeutic Area Head, Pain & Pediatrics
Ms. Natasha Rogozenski	Director, Regulatory Affairs
Dr. Jack Singer	VP, Global Regulatory Affairs, CNS
Dr. Julia Wang	Associate Director, Statistics Leader
Dr. QinYing Zhao	Assoc. Dir., Global Clin. PK & Clin. Pharmacology Leader
<b>FDA HFD-170</b>	<b>Title</b>
Bob Rappaport, MD	Division Director
Sharon Hertz, MD	Team Leader, Analgesics
Thomas Permutt, PhD	Team Leader, Statistics
D. Elizabeth McNeil, MD	Medical Reviewer
Joan Buenconsejo	Statistics (observing)
Lisa Basham-Cruz, MS	Regulatory Project Manager

### Meeting Minutes:

Following introductions, Dr. Paul, of Grunenthal noted that the representatives from Johnson and Johnson serve as partners in the development of this compound and may participate fully in the discussion. Dr. Hertz welcomed the sponsor and noted that the preclinical program is insufficient at this time and should be addressed at a later date. The discussion then moved to the questions submitted in the October 8, 2003, meeting package. The questions are presented below in italicized text. Agency responses, prepared prior to the meeting and presented on slides, are bolded. Discussion is presented in normal text.

#### *Question 1 (chronic pain indication)*

*Does the Division agree that the proposed Phase IIb trial designs in the osteoarthritis and low back pain protocol synopses included in the information package may be considered adequate to determine the dosage to be used in Phase III trials?*

#### FDA RESPONSE

- **If the Phase IIb trials show that CG5503 is more efficacious than placebo, they will inform dosing for the pivotal trials.**
- **It is necessary to establish a minimum effective dose and, if appropriate, a maximum effective dose for the modified-release product.**
- **The proposed trial design for Phase 3 could result in a high dropout rate from the placebo group. One approach for the analysis of this data would be a responder analysis.**
- **It may be worthwhile to consider exploring the use of a responder analysis during these Phase 2 trials.**

The sponsor said that they have found comparable results in Phase 1 and Phase 2a and b studies using pharmacokinetic/pharmacodynamic (PK/PD) modeling. They also plan to perform the same modeling techniques for Phase 3 studies and inquired whether this is acceptable. Dr. Lee responded that he would need to see the modeling plan before determining its acceptability. He also suggested that the sponsor submit the proposed Phase 2 designs for review. The sponsor asked whether a titration design is acceptable. Dr. Hertz responded that a titration design will support the final titrated dose, but if the starting dose is high, e.g. 100 mg, and effective, then some means to assess the efficacy of the 50-mg dose will need to be considered. The sponsor asked whether the titration dose could be approved if shown to be useful for safety and tolerability, but not effectiveness. Dr. Hertz responded affirmatively. Dr. Rappaport clarified that the labeling will not state that the titration dose is effective, but only useful as a titration step. The sponsor asked whether, if all the doses show efficacy, the lower doses should be tested in Phase 3 studies. Dr. Hertz responded affirmatively, and added that efficacy findings from all doses must either be replicated, or supported by appropriate PK modeling.

The sponsor asked for more information on the "responder analysis." Dr. Permutt explained that this analysis serves both as a way to make the outcomes easily interpretable from a clinical

standpoint and as a way of dealing with problems of missing data. In summary, criteria are established for success and failure and, based on these criteria, subjects are categorized as successes or failures. This helps with the missing data problem in that those with missing data are considered failures. The sponsor inquired whether this should be a primary outcome measure in Phase 3 trials. Dr. Permutt agreed, but said that it would be worthwhile to explore this method during Phase 2, as well. The sponsor said that they will proceed as previously planned with the phase 2 studies, but use a responder analysis as an exploratory measure. They asked what criteria they should choose for successful pain treatment. Dr. Hertz responded that the criteria should consist of clinically meaningful outcome measures such as pain intensity, pain relief, and when part of the protocol, use of rescue medication. Dr. Permutt stated that the statisticians would be available to offer advice on the model. The sponsor asked whether the Division would be open to combined outcomes, e.g., pain relief and improvement in function. Dr. Hertz responded that use of secondary outcomes that provide context for primary outcome measures such as pain intensity or pain relief are useful, but composite outcomes of different types of domains are not considered useful.

*Question 2 (Chronic pain indication):*

*Are the inclusion/exclusion criteria for the proposed Phase IIb studies acceptable to the division? Would these criteria be adequate in seeking an indication for moderate to severe pain? Will the severity of mean pain intensity defined as greater than or equal to 50 mm VAS support the indication of moderate to severe pain?*

**FDA RESPONSE**

- **The inclusion criteria as defined would be acceptable for an indication for moderate-severe pain.**
- **The inclusion/exclusion criteria allow participation of opioid experienced patients. They should be monitored for signs of withdrawal during the washout period.**

The sponsor asked whether the Division had any objections to any of the inclusion/exclusion criteria. Dr. McNeil responded that the Division does not have any objections. The sponsor then asked whether their increase in pain measure from 40 mm to 50 mm is acceptable for a moderate to severe pain indication. Dr. McNeil responded affirmatively. The sponsor asked how inclusion of people with history of seizure or head trauma would effect labeling. Dr. Hertz said that this information is informative and that exclusion of such patients would result in the loss of an opportunity to explore this patient population. If there is a reason to exclude this population, then it is appropriate to do so, and this would be reflected in the labeling. If there is no reason to exclude them at this time, however, then it is appropriate to obtain general experience with the drug. The sponsor inquired about concomitant drug use during the trial. Dr. Hertz responded that this needs to be explored, unless there is a specific reason to think it may interfere with the demonstration of efficacy. The sponsor stated that they have no evidence of drug-drug interactions (DDI) and inquired whether any models exist to explore this. Dr. Lee said that there are no specific models, but encouraged the sponsor to propose a strategy. He continued that additional clinical pharmacology data is needed about the drug's metabolism, activity of its metabolites, etc. This should be explored first. Once the clinical pharmacology of the drug is better understood, then DDI may be more effectively explored.

Dr. Lee addressed other general clinical pharmacology comments.

#### Clinical Pharmacology Comments

- Multiple dose PK information should support the dose(s) selected for the Phase 3 pivotal trials
- Please be aware of the Clinical Pharmacology comments discussed during Pre-IND meeting (11/17/2000)

Dr. Lee told the sponsor to utilize data obtained during the multiple dose PK analysis that is ongoing to inform dosing, etc., in the Phase 3 trials. To date, all dosing has been single-dosing. Information is needed to justify multiple dosing in Phase 3 trials. Dr. Hertz asked whether the sponsor had a sense of the degree to which this drug behaves as an MAOI. The sponsor clarified that this drug is not an MAOI, but a norepinephrine reuptake inhibitor and is 100-fold weaker than NSRI.

The discussion returned to labeling issues regarding the inclusion/exclusion criteria. Dr. Rappaport summarized that the manner in which these issues affect labeling depends on weight of evidence. The sponsor inquired again about the exclusion of concomitant medications and how this may affect labeling. Dr. Hertz responded that it is acceptable to exclude concomitant medications if it is necessary to demonstrate efficacy. Products excluded due to concerns about PK/PD interactions, however, are of concern and, in some manner, the risk of these interactions must be addressed in the label.

#### *Question 3 (Chronic pain indication):*

*Are the proposed study durations for these Phase II studies acceptable to the Division?*

#### **FDA RESPONSE**

**The two week fixed dose period is acceptable in these exploratory, dose-finding studies. Studies intended to support a finding of efficacy in chronic pain will require a fixed-dose period of at least 12 weeks.**

The sponsor inquired whether the titration phase could be included in the 12-week period. Dr. McNeil clarified that the 12-week period would not include the titration phase and that there should be a fixed-dose period of 12-weeks. Dr. Hertz explained that it has been the Division's experience that some sponsors wish to use Phase 2 trials in support of efficacy. The trial, as planned now, would not suffice in this regard.

#### *Question 4 (Chronic pain indication):*

*Would the Division find the exclusion of identified placebo responders acceptable in Phase III studies?*

#### **FDA RESPONSE**

- A study design that excludes placebo responders could be acceptable. Review of the methodology would be required for further comment.
- Enrichment designs using responders to study drug is another alternative.

The sponsor asked for clarification on the concept of "enrichment design." Dr. Hertz explained that an enrichment design selects for responders. The sponsor's proposal to exclude placebo responders, although not before proposed to this division, could also be acceptable. Using an enrichment design should not have an impact on labeling. The sponsor said that they will define a placebo responder and further discuss their proposal with the Division.

*Question 5 (Chronic pain indication):*

*Is a double-blind treatment period of 3 months duration in Phase III studies in low back pain and osteoarthritis sufficient to support a claim for moderate to severe chronic pain?*

**FDA RESPONSE**

- Yes

The sponsor noted that their cancer pain trial is a four-week study. Dr. Hertz said that this trial may be supportive of efficacy, but will not be considered pivotal due to the 12-week duration requirement. The trials will be described in the label. Dr. Hertz went on to say that the sponsor need not conduct two studies in each type of pain to fulfill the replication requirement unless a particular indication is desired. A general indication for moderate to severe pain does not require replication in each type of pain, but rather a replicated demonstration of efficacy.

The sponsor asked whether the Adverse Event (AE) section of the label would list separate AEs for osteoarthritis and low back pain. Dr. Hertz responded that this is not normally the case unless the populations respond differently to the drug. The sponsor asked whether they may list the AEs of active comparators. Dr. Hertz said that this would not be allowed. Comparative claims carry a high burden of proof and must be replicated. Any mention of comparative data will be removed completely from the label unless there is an adequate body of evidence to justify its inclusion. The sponsor asked what would qualify as a superiority claim. Dr. Hertz responded that if one determined the equipotency of two drugs and then determined that the test drug had a quicker onset of action, worked better, or had less AEs associated with it, then this may be adequate to demonstrate superiority. This demonstration, however, must be replicated, and is not necessarily achievable in the two studies intended to support efficacy. The sponsor asked about the policy on comparative data as it relates to promotional material. Dr. Hertz said that that would need to be evaluated by the Division of Drug Marketing and Communication (DDMAC). Dr. Permutt clarified that a replicated head-to-head comparison of study drug with a comparator would be required to obtain a superiority claim.

The sponsor asked whether inclusion of a comparator in pivotal trials is necessary for assay sensitivity. Dr. Hertz responded that the inclusion of a comparator is useful for obtaining conversion information. Dr. Permutt added that assay sensitivity is not an issue if the study drug beats placebo. Inclusion of a comparator is useful, however, if the study drug "fails" and a comparator of known efficacy also "fails." Results such as this may not lead to a conclusion that the study drug failed, but that the study may have been flawed. The sponsor asked whether the

PK/PD relationship should be observed in the studies. Dr. Hertz responded that evaluation for such a relationship is useful, but it is often difficult to demonstrate a PK/PD relationship during a chronic pain trials. Furthermore, for some drugs there is no PK/PD correlation per se.

Dr. Permutt addressed the statistical question.

*Question 6 (Chronic pain indication):*

*In order to meet ICH E1A guidelines for chronic safety, the sponsor proposes to pool safety data and subject exposures from trials conducted in the US and Europe. Does the Division accept this concept of pooling across pain models and geographic regions?*

#### **FDA RESPONSE**

- **Pooling is acceptable.**
- **The data must be presented so that different pain models or geographic regions could be evaluated separately as well.**
- **A justification for this pooling would have to be provided in the application.**

Dr. McNeil continued with the clinical questions.

*Question 7 (Chronic pain indication):*

*Does the Division concur with the Sponsor's intent to satisfy ICH guideline E1A for chronic safety by assessing 300 patients treated for six months and 100 patients treated for 1 year?*

#### **FDA RESPONSE**

- **The safety database must include at least 300-500 patients treated for six months and at least 100 treated for one year at the proposed commercial doses.**
- **The total number of patients treated should be 1500 at a minimum.**

The sponsor asked whether they would need 1500 patients exposed to each approved dose. Dr. Hertz responded that 1500 total patients should be exposed to the drug, with most at the higher doses.

*Question 8 (Chronic pain indication):*

*Does the Division agree that the Sponsor can obtain a broad chronic indication of moderate to severe pain intensity by assessing study drug efficacy in chronic low back pain, osteoarthritis and cancer pain models during Phase III?*

#### **FDA RESPONSE**

- Yes

*Question 9 (Chronic pain indication):*

*Is the primary endpoint in both synopses adequate to measure clinically meaningful differences between the treatment arms, active control and placebo?*

**FDA RESPONSE**

- Yes.

*Question 1 (Acute pain indication):*

*Are the two proposed acute pain models (bunionectomy and total hip replacement surgery) acceptable to the Division for Phase III trials supporting a general acute pain indication?*

**FDA RESPONSE**

- Yes.

*Question 2 (Acute pain indication):*

*Does the Division find the proposed Phase IIb trial designs in bunionectomy and orthopedic surgery acceptable to identify the dosage for Phase III trials supporting a general acute pain indication?*

**FDA RESPONSE**

- The trials are appropriate for dose finding purposes.
- It may not be necessary to replicate the bunionectomy and orthopedic surgery studies if sufficient information can be provided from the studies described.
- **Sufficient information would consist of data to support efficacy from the repeated dosing periods, characterization of the dosing interval, minimum effective dose, maximum tolerated and effective dose, data to explore dose-response characteristics, and a sufficient number for evaluation of safety.**

The sponsor inquired whether the minimum effective dose and maximum effective dose may be determined using PK/PD modeling. Dr. Lee said that a proposal should be submitted for review. The sponsor asked if the Division would need different dosing intervals tested or whether PK information to support the dosing interval would be adequate. Dr. Hertz responded that using PK information alone may be problematic, because the therapeutic range of plasma levels may not be demonstrated during development, particularly if there is no PK/PD relationship. PD information can be difficult to interpret as well. The drug should be adequately characterized for how quickly it works, how long it lasts, and how often patients need to be redosed (or rescued). In addition, there must be adequate safety information on the dosing interval. The sponsor proposed that they perform their acute Phase 2 studies with flexible dosing and then more firmly

establish the dosing interval during Phase 3 studies. Dr. Permutt suggested that pharmacokinetic data might prove helpful in selecting a dosing interval to be tested in studies of a fixed regime. Single-dose trials also provide information about the effect of the drug over time and the use of rescue. While this does not directly test the effect of dosing intervals, it provides good information from which to build. The sponsor responded that with postoperative pain, pain intensity is high on the first day, but decreases later. They are concerned that with a fixed-dosing interval, the patients will be undertreated on the first day, and overtreated later. Dr. Permutt said that it is not wise to use flexible dosing in clinical trials because these drugs are significantly toxic. There may be some evidence of efficacy and some evidence of toxicity, but insufficient evidence of a favorable balance of benefit to risk at any given dose. The sponsor summarized the discussion by saying that they should conduct fixed-dose studies to establish efficacy and use secondary parameters, e.g., drop out rates, use of rescue, to adjust the dosing interval. Dr. Rappaport said that it is a good idea to explore dosing interval during Phase 2 studies and to use that information to plan Phase 3 efficacy studies.

The sponsor asked about the Division's currently preferred labeling language for moderate to severe pain. Dr. Hertz responded that current standard language is "for treatment of moderate to severe pain." She added that the modified-release opiates have required an extended indication due to the risks of abuse and diversion. The specific language for the indication will be determined based on the drug's risk, potency, etc. To this end, Dr. Hertz advised the sponsor to conduct an abuse liability assessment. The sponsor asked about the specific language in the OxyContin label that contraindicates its use during the first 24 hours of the postoperative period. Dr. Hertz responded that OxyContin is not indicated for acute use. If the sponsor demonstrated that CG5503 is safe during the immediate post-operative period, then it may be appropriate to indicate it for that use. If use during this period is not supported, it will be excluded from the label. The sponsor said that they have single-dose data from the first 8 hours after surgery to the day after, and asked whether they should go back and study the first 8 hours if they do not want that time period excluded from the label. Dr. Hertz responded affirmatively, and added that, in this case, the label may say that the drug is appropriate for use in the post operative setting when oral opiates are appropriate.

*Question 3 (Acute pain indication):*

*Are the proposed study durations acceptable to the Division?*

#### **FDA RESPONSE**

- **The study durations are appropriate for an acute pain indication.**

*Question 4 (Acute pain indication):*

*Are the proposed inclusion/exclusion criteria for the Phase IIb studies acceptable to the Division?*

#### **FDA RESPONSE**

- **Yes.**

*Question 5 (Acute pain indication):*

*What are the Division's requirements regarding the size and duration of the clinical safety database for an acute pain indication?*

**FDA RESPONSE**

- At least 1500 patients since this is a NME
- However, it may be possible to use data from the modified-release formulation to supplement the safety database.

Dr. Hertz explained the last point by saying that if the modified-release formulation is submitted prior to the immediate-release formulation, the data from the modified-release may be used in the immediate-release application. More than 500 patients must be included in the safety database for the immediate-release unless a safety signal appears. In this case, many more could be required. If the immediate-release is developed first, then further discussion would be needed as to the number of safety exposures required.

*Question 6 (Acute pain indication):*

*At the end of Phase II, assuming we have positive data in the following acute studies: one single-dose bunionectomy study, one multiple-dose bunionectomy, one multiple-dose total hip replacement study and two single-dose dental extraction studies would replication of the bunionectomy and total hip replacement studies be sufficient in Phase III for a general acute pain indication?*

**FDA RESPONSE**

- Yes.

*Question 7 (Acute pain indication):*

*Is a flexible dosing regimen acceptable as a basis for the elucidation of optimal dosing and would this be an acceptable study design approach for replicate study designs in Phase III?*

**FDA RESPONSE**

- A study using titration to effect as the dosing paradigm can provide useful information when this compliments data from fixed dose, parallel arm studies.
- It is necessary to establish a minimum effective dose and the maximum safe and effective dose for this product.

Dr. Rappaport emphasized the need for an abuse liability assessment for this compound. As a new opiate, there will be enormous scrutiny. A risk management plan will be needed, and there will likely be some form of "class labeling" for modified-release opiates.

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The sponsor asked for clarification on the pharmacology/toxicology issue raised at the beginning of the meeting. Dr. Hertz responded that the pharmacology/toxicology reviewer (not present) did not find adequate preclinical data to support the duration proposed for the Phase 3 clinical trials.

The sponsor asked whether there is a standard set of requirements for an abuse liability assessment. Dr. Hertz encouraged the sponsor to develop a proposal for consideration by the Division. The sponsor asked whether abuse liability should be considered during Phase 2 or 3 trials. Dr. Hertz responded that consideration for an abuse liability assessment should begin as early as possible. The Division welcomes proposals and will provide guidance.

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Lisa E. Basham-Cruz  
Regulatory Project Manager

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