

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-304

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 04/30/10 <i>See OMB Statement on Page 3.</i>	
		NDA NUMBER 22-304	
		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) TBD			
ACTIVE INGREDIENT(S) Tapentadol HCL		STRENGTH(S) 50mg, 75mg, 100mg	
DOSAGE FORM 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 only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: 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.			
FDA will not list patent information if you file 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.			
1. GENERAL			
a. United States Patent Number RE 39,593E (Reissue of US 6,248,737)		b. Issue Date of Patent April 24, 2007 (US 6,248,737 issued June 19, 2001)	c. Expiration Date of Patent June 19, 2018
d. Name of Patent Owner Grünenthal 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) <input checked="" type="checkbox"/> Joseph D. Evans		Address (of agent or representative named in 1.e.) Crowell & Moring, P.O. Box 14300	
		City/State Washington, D.C.	
		ZIP Code 20044-4300	FAX Number (if available) 202-628-8844
		Telephone Number 202-624-2500	E-Mail Address (if available) jdevans@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? (see attached note) 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) 3,86,88,90,93,94,95,96,98,100,103,105,106,110, 112,114,117,136,137,138,140 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? Yes 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 approved labeling.) **TRADENAME** is indicated for the relief of moderate to severe acute pain.

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	
<p>6.1 <i>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.</i></p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
<i>Ellen Coletti</i>	1-15-08
<p>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).</p>	
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 Ellen Coletti	
Address Johnson & Johnson One Johnson & Johnson Plaza	City/State New Brunswick, NJ
ZIP Code 08933	Telephone Number 732-524-2359
FAX Number (if available) 732-524-5889	E-Mail Address (if available) ecoletti@corus.jnj.com
<p>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:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

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 supplemental 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/opacon/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.

Attachment for Form 3542a (U.S. Patent No. RE 39,593)

- 2.2 Applicants understand the term "claim" as used in this question to mean a claim limited to one or more different polymorphs of the active ingredient described in the NDA, and with this understanding, the answer is no. Accordingly, submission of the additional test data is not necessary.**

11/20/08

EXCLUSIVITY SUMMARY

NDA # 22-304

SUPPL #

HFD # 170

Trade Name <none>

Generic Name tapentadol

Applicant Name Ortho-McNeil-Janssen-Pharmaceuticals, Inc.

Approval Date, If Known 11/20/2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

Five

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

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

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

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

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

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

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

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

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

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

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

YES NO

If yes, explain:

Name of person completing form: Matthew Sullivan
Title: Regulatory Project Manager
Date: November 19, 2008

Name of Office/Division Director signing form: Bob A. Rappaport
Title: Director, Division of Anesthesia, Analgesia and Rheumatology 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.**

/s/

Bob Rappaport
11/20/2008 05:39:57 PM

11/20/08

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22304 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: 11/20/08 Stamp Date: 1/23/2008

Proprietary Name: <none>

Established/Generic Name: Tapentadol

Dosage Form: Tablets (Immediate Release)

Applicant/Sponsor: Johnson and Johnson

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

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

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Management of acute moderate to severe pain

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

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

(b) No. PREA does not apply. **Skip to signature block.**

** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.*

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed [‡]
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input checked="" type="checkbox"/> Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/> Other	0 yr. 1 mo.	17 yr. __ mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): 06/30/2016						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

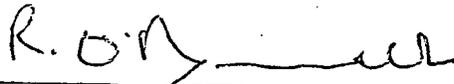
Matthew Sullivan
11/20/2008 03:09:24 PM

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

**DEBARMENT CERTIFICATION
TAPENTADOL HYDROCHLORIDE**

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

16 JAN 2008

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-304 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: <none> Established/Proper Name: Tapentadol HCl Dosage Form: oral tablets Strengths: 50 mg, 75 mg, 100 mg		Applicant: Ortho-McNeil-Janssen-Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Matt Sullivan, MS		Division: HFD-170, Division of Anesthesia, Analgesia and Rheumatology Products
<p>NDA: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		Nov 23, 2008 Nov 20, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None

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

<p>❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application² Characteristics</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <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 </p> <p>Comments: _____</p>	
<p>❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____</p>	<p>10/8/08; 11/20/08</p>
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes, date
<p>❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

Answer the following questions for each paragraph IV certification:

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

Yes No

(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)?

Yes No

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?

Yes No

(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)?

Yes No

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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist³</p>	<p>11/21/08</p>
Officer/Employee List	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) Approval: 11/20/2008</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>1/22/2008</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	11/20/08
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP 9/25/08 <input checked="" type="checkbox"/> DRISK 11/20/08 <input checked="" type="checkbox"/> DDMAC 3/12/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD 10/29/08
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	DMEPA: 9/25/08 DR Letter: 9/30/08
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	RPM Filing Review: 11/4/08
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable 10/8/08
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable 9/11/08
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 6/28/07
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 9/22/06
• Other (e.g., EOP2a, CMC pilot programs)	EOP2a: 1/11/06 & 1/13/06
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/20/08
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/16/08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/17/08
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	9/22/08; 11/20/08
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	9/22/08 Clinical Review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	9/22/08 Clinical Review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None TQT Study Review 7/17/08
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 10/17/08
❖ Risk Management	<input type="checkbox"/> None
• 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>)	6/26/08 - OSE Review 11/21/08 - REMS Memo
• REMS Memo (<i>indicate date</i>)	
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	11/11/08; 11/18/08
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 9/12/08
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/3/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 9/30/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/19/08
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/6/08; 10/23/08; 11/20/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9/24/08; 10/23/08
❖ 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 type="checkbox"/> No carc 9/10/08 (2)
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 8/26/08 (Minutes: 9/2/08) Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/2/08
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 2/12/08; 7/21/08; 9/30/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None DOE (Design of Experiment): 9/11/08
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	

<input checked="" type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	7/11/08; 7/18/08
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: 2/25/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

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Appendix A 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.

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

/s/

Matthew Sullivan
11/21/2008 05:23:00 PM

11/18/08

MEMORANDUM

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

DATE: November 17, 2008

TO: File

FROM: Matthew Sullivan, MS, Regulatory Project Manager

SUBJECT: **Pre-Approval Safety Conference**
NDA 22-304, Tapentadol 50, 75 and 100 mg Tablets

In lieu of a separately scheduled preapproval safety conference with OSE staff, the Division chose to include OSE staff in the planned review division meeting. OSE staff members were invited, and attended, the Wrap-Up meeting for NDA 22-304, on September 11, 2008. Members of OSE staff present at the meeting were Chris Wheeler, Regulatory Project Manager, Lauren Lee (Choi), Lead Pharmacist, Gita Akhavan-Toyserkani, Safety Evaluator, and Afrouz Nayernama, Safety Evaluator. Also present were the following: Curt Rosebraugh (phone), Bob Rappaport (phone), Sharon Hertz, Rob Shibuya, Ellen Fields, Dionne Price, Jon Norton, Adam Wasserman, Kathy Young, David Lee, John Hill, and Lori Love.

During the meeting, the Dr Fields (Clinical Reviewer) gave a comprehensive overview of the clinical studies, adverse events, safety concerns, and potential post-marketing requirements. The Medical Officer's presentation was forwarded prior to the meeting to Chris Wheeler, and the final review was sent soon after the meeting. Dr Fields noted that the safety was similar to other Schedule II opioids, and there was no apparent increased seizure risk as with Tramadol, a pharmacologically similar product. No other safety signals were detected during this review.

OSE was asked if they had identified any needs for post-marketing activities or post-approval safety monitoring. Dr Akhavan-Toyserkani of OSE replied that they had not identified any such need. Furthermore, the need for a REMS was briefly discussed, and there was consensus that as an immediate-release oral opioid, no REMS was needed at the current time.

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Addendum to Pre-Approval Safety Conference minutes

Subsequent to the September 11, 2008, Pre-Approval Safety Conference, a decision was made, in consultation with the Controlled Substance Staff, that a Medication Guide (MG) was necessary to ensure the safe use of this product. The need for this MG also triggered the implementation of a REMS, although the MG was the only aspect of the REMS considered necessary at this time.

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this page is the manifestation of the electronic signature.**

/s/

Matthew Sullivan
11/18/2008 12:41:40 PM
CSO

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: RE: labeling meeting
Date: Monday, November 03, 2008 10:53:00 AM

I just spoke with the DMEPA folks about the carton PDFs.

If you're planning to NOT market until you get a tradename, then you should submit new PDFs showing "TRADENAME" or "XXXXX" as a place holder for the name. If you ARE planning to market without a name, then go ahead and submit PDFs just showing "Tapentadol HCl".

Is that what you were planning anyway? Just didn't want there to be confusion.

Matt

From: Sullivan, Matthew
Sent: Monday, November 03, 2008 10:21 AM
To: Young, Kathleen A
Subject: RE: labeling meeting

Hi Kathy –

We're going to cancel the one today, but we should have the label back from the Sponsor on Thursday, and so we'll be able to review their comments at that time.

Matt

From: Young, Kathleen A
Sent: Monday, November 03, 2008 8:27 AM
To: Sullivan, Matthew
Subject: RE: labeling meeting

Hi, Matthew. Is there a labeling meeting today (Nov 3) at 1:30, and again on Thursday at 1-2? Thanks. Kathy

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: peds plan and label
Date: Friday, October 31, 2008 3:25:00 PM
Attachments: N22304 draft labeling.doc

Katie –

Attached is the draft label. We have used "track changes" to reflect any additions or deletions from the label that you originally submitted. Please "accept" any changes that you agree with. If you don't agree with a change, please provide an alternative (or ask us a clarifying question using the comment feature).

I should note that this label hasn't been cleared by upper management yet, so additional changes may still be forthcoming.

Additionally, we have the following comments on your pediatric plan.

We have reviewed your response to the October 8, 2008 comments on the proposed pediatric plan, and have two additional comments, as follows:

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We'd like to have your label and revised pediatric plan back by noon on Wednesday.

Thanks
matt

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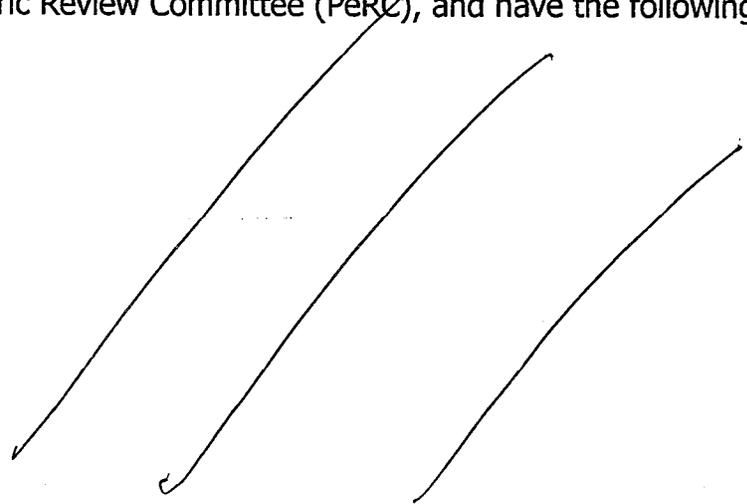
From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: Peds information N22304
Date: Wednesday, October 08, 2008 12:06:00 PM

Hi Katie –

Give me a call when you have a minute.

Matt

We have reviewed your proposed pediatric plan in conjunction with the Pediatric Review Committee (PeRC), and have the following comments:



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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: another pediatric item tapentadol N22304
Date: Friday, September 26, 2008 4:41:00 PM

Katie –

Another pediatric item that just came up. This was emailed to me by the pediatric team that's looking at the deferral request.

Ideally, you could include this with your pediatric certification letter. I think all that's needed is to provide more specific dates around the pediatric plans (e.g., instead of 2Q 2010, you should list June 30, 2010).

Pediatric Plans do not have to include the entire protocol. However, they must include a general description of the studies to be conducted (can be as simple as "a randomized, double blind, placebo control dose ranging study in patients 12-16 years"), the date they plan to begin enrollment, the date they plan to begin the studies, and the date they plan to submit the studies.

Please let me know if this makes sense, and when you think you can get something to me.

Matt

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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: Clin Pharm IR, 9/12/08
Date: Friday, September 12, 2008 10:28:00 AM

Sorry that these keep coming ☺

In the draft package insert, in patients with severe renal impairment you are proposing that tapentadol IR tablet use is 'not recommended.' We understand that in severe renal impairment, tapentadol pharmacokinetics are not affected but that tapentadol-O-glucuronide is likely to accumulate significantly. However, in light of the fact that tapentadol-O-glucuronide is an inactive metabolite, please explain your basis for not recommending the use of tapentadol in severe renal impairment subjects.

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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: Clinical IR 9/10/80
Date: Wednesday, September 10, 2008 5:59:00 PM

Katie –

A clinical IR for you...hopefully not many more. (and if you are able to provide me with a eCTD reference to where we can find this information, then it really isn't an info request at all – that is, no official response on your part would be required.)

"One subject was identified in Table 77SU (Hepatic SMQ for Phase 2/3 DB) as having possible drug-related hepatic disorder-severe events only, in the all tapentadol group. Please provide location of the narrative for this subject, or provide a narrative if there is not one in the submission."

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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
"Ferrone, Peggy [PRDUS]";
Subject: RE: Clinical Information Request tapentadol 9/2/08
Date: Tuesday, September 02, 2008 2:48:00 PM

And another; from the Clinical Pharmacology group....

Our review of data submitted in support of tapentadol as a BCS class I drug is currently ongoing. To facilitate this, submit the following;

1. Gastrointestinal stability data for tapentadol. This can be inferred based on the stability of the compound in simulated gastric and simulated intestinal fluids.
2. CaCO₂ Cell Study PK744 lacks internal standards (e.g., low, medium, and high permeable drugs) to validate the results. If there are information from any other other CaCO₂ Cell study(ies) that contain internal standards, submit these to the NDA.

Please refer to the Agency's Guidance on "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" for further information"

From: Sullivan, Matthew
Sent: Tuesday, September 02, 2008 9:34 AM
To: 'Dusek, Kathleen [PRDUS]'; Ferrone, Peggy [PRDUS]
Subject: Clinical Information Request tapentadol 9/2/08

Good morning –

Here's a clinical IR to start out your day:

Please submit:

1. Table displaying discontinuations from studies due to abnormal vital signs by Phase (Phase 1, Phase 2/3) , similar to that provided for discontinuations due to abnormal labs. Include narratives or links to existing narratives for these subjects.

2. Table displaying discontinuations from studies due to abnormal ECGs by Phase (Phase 1, Phase 2/3) , similar to that provided for discontinuations due to abnormal labs. Include narratives or links to existing narratives for these subjects.

Thanks
Matt

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Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Ferrone, Peggy [PRDUS];
Subject: Clinical Information Request tapentadol 9/2/08
Date: Tuesday, September 02, 2008 9:34:00 AM

Good morning –

Here's a clinical IR to start out your day:

Please submit:

1. Table displaying discontinuations from studies due to abnormal vital signs by Phase (Phase 1, Phase 2/3) , similar to that provided for discontinuations due to abnormal labs. Include narratives or links to existing narratives for these subjects.

2. Table displaying discontinuations from studies due to abnormal ECGs by Phase (Phase 1, Phase 2/3) , similar to that provided for discontinuations due to abnormal labs. Include narratives or links to existing narratives for these subjects.

Thanks
Matt

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Phone 301-796-1245
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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]"; Ferrone, Peggy [PRDUS]; "PFERRONE@its.JNJ.COM";
Subject: Tapentadol IR 8/25/08
Date: Monday, August 25, 2008 5:10:00 PM

Hi Peggy and Katie –

(Peggy – I assume that your email is now "@its.jnj.com" but I'm not sure, so I'm sending this to both accounts)

Please find below a clinical information request:

Provide a narrative for subject #100567, including the subject's medical history, concomitant medications, duration and dose of tapentadol administration, reason for obtaining troponin levels, and troponin level results and dates.

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matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: CMC IR 8/7/08
Date: Thursday, August 07, 2008 10:45:00 AM

Katie –

A CMC information request, which I believe is related to the drug product quality control. I inadvertently sat on this request, thinking it was for something else, so a prompt reply is appreciated.

Oh, and please confirm receipt, just in case.

Thanks
Matt

1. Describe the concentration and amount of [redacted] proposed for the commercial scale [redacted] step in Section 3.2.P.3.3 "Description of the Manufacturing Process and Process Control".
2. Provide justification with data for the proposed operating parameter range for the [redacted] listed in Table 1 of Section 3.2.P.3.3

b(4)

b(4)

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From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: RE: NDA 22-304, Tapentadol HCl - Information Request 31 July 2008, Clarification Request
Date: Monday, August 04, 2008 5:21:00 PM

Katie –

Here is the nonclinical IR. I guess you should probably confirm receipt of this email, just in case.

Thanks
Matt

Please provide TK or PK data on the specific doses used in the Wistar rats (3, 6, and 12 mg/kg/day IV) for the Segment 1 (fertility) study to support your stated multiples in the label.

From: Dusek, Kathleen [PRDUS] [mailto:KDusek@PRDUS.JNJ.COM]
Sent: Monday, August 04, 2008 11:07 AM
To: Sullivan, Matthew
Subject: FW: NDA 22-304, Tapentadol HCl - Information Request 31 July 2008, Clarification Request

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

From: Dusek, Kathleen [PRDUS]
Sent: Friday, August 01, 2008 11:31 AM
To: Sara Stradley (E-mail)
Cc: Matthew Sullivan (E-mail)
Subject: NDA 22-304, Tapentadol HCl - Information Request 31 July 2008, Clarification Request

Hi Sara,

We need some clarification on the second request from July 31st (Provide a table of potentially important lab values by treatment group and dose received for tapentadol IR and placebo).

Potentially clinically important lab values are defined in the 4 month safety update ISS SAP (page 22, table 7). Summary tables of the number of subjects who met this criteria are provided in the Attachments of the Summary Document as DLAB02a (Attachment 3.10.2SU) , DLAB02b (Attachment 4.8.2SU), DLAB03 (Attachment

3.10.3SU), DLAB06a (Attachment 3.10.6SU), and DLAB06b (Attachment 4.8.4SU). The column headings for multiple-dose, double-blind tables are: Placebo, TAP 0-30 mg, TAP >30-60mg, TAP >60-90mg, TAP >90-120mg, TAP Flexible Dose, All Tapentadol . As specified in the ISS SAP, studies KF5503/04 and KF5503/08 are excluded from summary tables for multiple-dose, double-blind studies due to large variations of the reference ranges for these studies versus studies KF5503/21, KF5503/22, PAI-3002, PAI-3003, PAI-3004, PAI-3001 and KF5503/37.

Is this sufficient to address the request? If not, please ask the Reviewer to clarify what is needed (e.g., column headings).

Thanks.

Katie

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ON ORIGINAL**

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: Info request for Tapentadol NDA
Date: Monday, July 21, 2008 5:10:00 PM

Hi Katie –

I just got the response to the ITT information request – thanks.

Here is another one:

1. Provide Shift Tables for clinical laboratory evaluations and vital signs by treatment for the complete phase 2/3 multiple dose double blind pooled analysis set and the Phase 3 open label extension safety analysis set.
2. Submit Table 2SU without the yellow highlights.

Matt

**APPEARS THIS WAY
ON ORIGINAL**

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: Information request for tapentadol 7/10/08
Date: Thursday, July 10, 2008 4:11:00 PM

Hi Katie –

Here is an IR for you. Have a good weekend.

Matt

In the data provided from study R331333-PAI-3002 (KF5503/33), the following seven subjects are shown as having completed the study yet are not included in the intent-to-treat (ITT) analysis set: 201716, 201988, 202126, 202166, 202206, 204495, and 204714. Please provide an explanation for why each of these subjects was excluded from the ITT analysis set, along with case report forms and other relevant supporting documentation.

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ON ORIGINAL

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Ferrone, Peggy [PRDUS];
Subject: Clinical Information Requests 6/13/08
Date: Friday, June 13, 2008 12:07:00 PM

Hi all –

I have some more clinical information requests for N 22-304 (below), and one general request related to the recent 120-day safety update.

The general request is this: Despite me saying it would be acceptable, it appears that the yellow highlights (denoting new information) in the safety update is distracting and difficult for the review team to work with. Would it be possible to resubmit the ISS without the yellow highlights? Sorry to have to ask you to do that.

Thanks
Matt

1. Tables similar to Table 37SU from the 4-month safety update displaying TEAEs in at least **1%** and at least **5%** of Subjects in the "All" Tapentadol IR Group: Phase 2/3 Multiple-Dose double-blind.
2. Tables similar to Table 39SU from the 4-month safety update displaying TEAEs in at least **1%** and **5%** of subjects by Tapentadol IR dose group: Phase 2/3 Multiple dose double-blind.
3. A table similar to Table 43SU from the 4-month safety update displaying TEAEs leading to treatment discontinuation in **all subjects** in the "all" tapentadol IR group: Phase 2/3 Multiple dose double-blind. This table should include all discontinuations due to TEAEs, not just those occurring in more than 3 subjects.

Tables should be submitted without yellow highlights.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Ferrone, Peggy [PRDUS];
Subject: Information Request N 22304
Date: Wednesday, June 11, 2008 2:18:00 PM

Hi Katie and Peggy –

Please see below for a clinical information request:

In the 4-month safety update you state that subjects randomized at site 011006 in study KF5503/31 were excluded from Phase 2/3 Multiple Dose Double Blind Safety analysis set and the Open-Label Extension Safety Analysis set due to data irregularities discovered during an audit. Please provide information regarding the results of the audit and the numbers and types of data irregularities. Also inform us whether data from these subjects were included or excluded from efficacy assessments. Please also include tables of adverse events for the excluded subjects.

Thanks
Matt

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Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: tapentadol information request 4/30/08
Date: Wednesday, April 30, 2008 2:03:00 PM

Katie –

Please see below:

Please provide the original study protocol issued May 24, 2006 for study **R331333PAI3002 (J&JPRD); KF5503/33 (Grünenthal); Phase 3.** The protocol submitted in section 5.3.5.1.1 is the one issued with Amendment INT-4 (August 29, 2007).

APPEARS THIS WAY
ON ORIGINAL

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: NDA 22-304 Clinical IR 3/25/08
Date: Tuesday, March 25, 2008 1:44:00 PM

Katie –

We are requesting an internal review of your Thorough QT study, HP5503/25.

There are a number of items that are needed for this review, and I hope you can help me gather all the necessary information.

Ideally, you would submit an amendment that contains the following items or direct links to the items previously submitted. If there is some reason why that wouldn't work, we can discuss alternatives.

Thanks
 matt

- Electronic or hard copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study.
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (Table 1, shown below)

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	

Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Michelle Safarik
3/12/2008 04:23:19 PM
DDMAC REVIEWER

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUST]";
Subject: NDA 22-304 Information Request 2/20/08
Date: Wednesday, February 20, 2008 5:15:00 PM

Katie

This one you can address via email; no submission is needed.

Thanks

Matt

Please provide a name and telephone contact at your foreign site, Janssen Pharmaceutica in Geel Belgium, where you perform drug substance manufacture steps 1-4 (from DMF 21084).

**APPEARS THIS WAY
ON ORIGINAL**

From: Sullivan, Matthew
To: "Dusek, Kathleen [PRDUS]";
Subject: 2/12/08 N22304 Information Request
Date: Tuesday, February 12, 2008 12:55:00 PM

Hi Katie –

Here is the first information request for Tapentadol.

1. Please provide narratives and case report forms for subjects discontinuing study HP5503/17 due to adverse events.
2. Please identify where in the submission the adverse event coding dictionary for the conversion of verbatim terms to preferred terms is located. If it is not in the original NDA, please submit it as an amendment.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

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

/s/

Matthew Sullivan
11/6/2008 10:32:51 AM
CSO

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-304 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: <none> Established/Proper Name: Tapentadol HCl Dosage Form: oral tablets Strengths: 50 mg, 75 mg, 100 mg		
Applicant: Johnson and Johnson / Ortho-McNeil-Janssen-Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: Jan 22, 2008 Date of Receipt: Jan 23, 2008 Date clock started after UN:		
PDUFA Goal Date: Nov 23, 2008	Action Goal Date (if different): Nov 20, 2008	
Filing Date: Mar 23, 2008 Date of Filing Meeting: Mar 7, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): Relief of moderate to severe acute pain		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>Refer to Appendix A for further information.</i>	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input 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 defaults to 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"/>	<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):	
List referenced IND Number(s): 61, 345	
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>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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 name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, explain:	
If yes, has OC/DMPQ been notified of the submission?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<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>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES # years requested: Five <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. 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)).</p> <p>3. 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))?</p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

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).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? *Check the Electronic Orange Book at: <http://www.fda.gov/cder/ob/default.htm>*

YES
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

Comments:

All paper (except for COL)
 All electronic
 Mixed (paper/electronic)

CTD
 Non-CTD
 Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

Comments:

If electronic submission, does it follow the eCTD guidance? (<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES
 NO

If not, explain (e.g., waiver granted):

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><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)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</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>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&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></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</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>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<u>PREA</u>	
<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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • <i>If yes, 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)</i> <p>Comments: Correct certification was not included with initial submission, but was submitted in the October 1, 2008, amendment.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <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)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): August 24, 2006 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): June 5, 2007 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 23, 2007

NDA/BLA #: 22-304

PROPRIETARY/ESTABLISHED NAMES: Tapentadol HCl

APPLICANT: Johnson and Johnson

BACKGROUND: NME. Not approved in any other country.
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matt Sullivan	Y
	CPMS/TL:	Sara Stradley	Y
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		Y
Clinical	Reviewer:	Ellen Fields	Y
	TL:	n/a	
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:	Laura Pincock	Y
	TL:	Kellie Taylor	Y
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Jon Norton	N
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kathy Young	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:	Meiyu Shen Atiar Rahman	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	John Hill	Y
	TL:	Ali Al Hakim	Y
Facility (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers	Lori Love, Sylvia Calderon (CSS)		

OTHER ATTENDEES: Sharon Hertz, Bob Rappaport, Curt Rosebraugh

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments: Sponsor did not submit color copies of proposed carton and container labeling. Sponsor was requested to do so, and they were submitted on March 13, 2008.</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</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"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <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> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable

<p>Comments:</p>	<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"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</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>PRODUCT QUALITY (CMC)</p> <p>Comments:</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"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Sterile product? <ul style="list-style-type: none"> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO • If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <ul style="list-style-type: none"> <input type="checkbox"/> YES <input type="checkbox"/> NO 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
FACILITY (BLAs only)	
Comments:	
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: ODE II (Curt Rosebraugh)	
GRMP Timeline Milestones:	
GRMP Review DUE	
<ul style="list-style-type: none"> - 1° and 2° reviews completed and signed in DFS:..... September 23, 2008 - CDTL memo completed (Package to Bob R):..... October 8, 2008 - Division Director Memo/package to Office (for NMEs):..... October 30, 2008 	
INTERNAL GO/November 20, 2008 PDUFA DATE:November 23, 2008	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. 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"/>	If BLA or priority review NDA, send 60-day letter.
<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.

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/s/

Matthew Sullivan
11/4/2008 02:33:22 PM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 10, 2008

TO: Matthew Sullivan, Regulatory Health Project Manager
Ellen Fields, M. D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products.

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-304

APPLICANT: Johnson & Johnson Pharmaceutical Research & Development

DRUG: Tapentadol Hydrochloride () **b(4)**

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Immediate release for the treatment of moderate-to-severe acute pain

CONSULTATION REQUEST DATE: March 21, 2008

DIVISION ACTION GOAL DATE: November 14, 2008

PDUFA DATE: November 23, 2008

I. BACKGROUND:

The review division requested inspection of three protocols KF5503/32: "A randomized, double-blind active-and placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of multiple doses of CG5503 immediate-release formulation in the treatment of acute pain from bunioectomy followed by a voluntary open-label extension"; protocol KF5503/33: "A randomized, double-blind, active-and -placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of multiple doses of CG5503 immediate-release formulation in subjects awaiting primary joint replacement surgery for end-stage joint disease"; and protocol KF5503/34 " A randomized, double-blind, active-control, parallel-group, 90-day safety study of CG5503 immediate release or oxycodone immediate release in subjects with chronic pain from low back pain or osteoarthritis of the hip or knee" of the investigational drug tapentadol hydrochloride [] performed for Johnson & Johnson Pharmaceutical Research & Development. The sponsor submitted results from the three protocols in support of NDA 22-304.

b(4)

The primary objective of the study protocol KF5503/32 was to demonstrate the efficacy of 3 doses of CG55030 immediate release (IR) versus placebo using the sum of pain intensity difference at 48 hour (SPID) to measure the analgesic effect and to assess the safety and tolerability of repeated doses of CG5503 IR over the double-blind treatment period in subjects with acute pain following bunionectomy; for study protocol SKF5503/33 was to determine the efficacy of CG5503 IR using the sum pain intensity difference (SPID) over 5 days compared to placebo, and to assess the safety and tolerability of multiple doses of CG5503 IR over a double-blind treatment period in subjects who are eligible for elective primary total or partial joint replacement of the hip or knee due to chronic osteoarthritis. Subjects participating in this pivotal trial will be evaluated for 10 days, using adverse events, pain scale intensity and significant changes in baseline laboratory measurements; and for protocol KF5503/34 was to evaluate the safety profile of CG5503 base IR 50 mg or 100 mg taken every 4 to 6 hours as needed over the long-term exposure of 90 days to provide adequate pain control with acceptable tolerability. Oxycodone IR 10 or 15 mg will be taken a 1 or 2 capsules as needed to provide adequate pain control and serve as a control to the investigational product CG5503 IR. The inspection targeted three domestic clinical investigators who enrolled a relatively large number of subjects and one foreign investigator. The sponsor was also inspected because the investigational product is a new molecular entity.

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ON ORIGINAL

II. RESULTS (by protocol/site):

Name of CI, IRB, or Sponsor site # and location	Protocol	Inspection Dates	Final Classification
Richard A. Pollak M.D. San Antonio, TX	KF5503/ 32	5/13-19/08	NAI
Ira J. Gottlieb, M.D. Pasadena, MD	KF5503/ 32	5/27-29/08	VAI
James P. Beretta, M.D. Birmingham, AL	KF5503/ 34	6/3-5/08	VAI
Marc Afilalo, M.D. Montreal, QC H3T1 E7 Canada	KF5503/ 33	7/14-17/08	NAI
Johnson & Johnson Pharmaceutical Research & Development	All 3 protocols	5/5-15/08	VAI

Key to Classifications

NAI = No deviation from regulations

VAI = deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication from the field; EIR has not been received from the field and complete review of EIR is pending.

**APPEARS THIS WAY
ON ORIGINAL**

Protocol KF5503/32

1. Richard A. Pollak, M.D.
Endeavor Clinical trials
8042 Wurzbach, Suite 450
San Antonio, Texas 78229

At this site, a total of 152 subjects were screened, 36 were reported as screen failures and the reason(s) were documented. 116 subjects were randomized, 18 subjects were discontinued, and 91 subjects continued on the open label extension phase of the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study.

The medical records for 20 subjects enrolled were reviewed in depth including drug accountability records and compared source document to case report forms and data listings for primary efficacy endpoint and adverse events.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Ira J. Gottlieb, D.P.M.
Chesapeake Research group
8028 Ritchie Hwy, Suite 100-104
Pasadena, MD 21122-1075

At this site, a total of 198 subjects were screened, 133 subjects were randomized and enrolled in the study. 65 subjects were reported as screen failures, 102 subjects completed the study and 31 subjects were withdraw/discontinued and the reason(s) were documented. The medical records for 19 randomized subjects' files were reviewed. Of the 19 subjects' file reviewed, 2 subjects were reported as screen failures, 3 subjects withdrew from the study due to lack of efficacy and 14 subjects completed the study.

The medical records/source data for 19 randomized subjects' files were reviewed in depth including drug accountability records and compared source documents to case report forms and data listings for primary efficacy endpoint and adverse events. Our investigation found subject 305140 (C) received prohibited

b(6)

medication (effexor) and the consent form is missing an essential element that the FDA may review the subjects' records.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol KF5503/34

3. James P. Beretta, D.O.
500 Cahaba Park Circle, First Floor
Birmingham, Alabama 35242

At this site, a total of 84 subjects were screened, 59 subjects were randomized, 25 subjects were reported as screen failures, 24 subjects completed the study and 35 subjects were terminated and the reason(s) were documented.

The medical records/source documents for all randomized subjects' files were reviewed in depth including drug accountability records and compared source documents to data listings and primary efficacy endpoints and adverse events. Our investigation found minor protocol deviations and a missing element in the informed consent.

In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol KF5503/33

4. Marc Afilalo, M.D.
SMBD Jewish General Hospital
Emergency Department Room D-012
3755, Cote Ste-Catherine Rd
Montreal, QC H3T 1E7
Canada

At this site, a total of 75 subjects were screened, 18 subjects were reported as screen failures and the reason(s) were documented. 57 subjects were randomized, 8 subjects were discontinued, and 49 subjects continued and completed the study. Informed consent for all subjects was verified.

The medical records/source data for 43 subjects' files were reviewed in depth including drug accountability records and compared source data to case report forms and data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate and found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application

5. Johnson & Johnson Pharmaceutical Research & Development
1125 Trenton Harbourton Road
P. O. Box 200
Titusville, New Jersey 08569-1504

The inspection audited Protocols R331332-PAI3002, R331333-PAI3003 and R331333- PAI3004 and focused on the following clinical investigators: Drs. Pollack, Gottlieb, Afilalo and Beretta.

The inspection reviewed the following: Company history and officers responsibilities, training program, manufacturing/design operations, manufacturing codes, test article , computerized system, selection of clinical investigators, quality assurance, clinical operations, study monitoring procedures, data review and reports, concomitant therapy, data safety monitoring board documentation, participating clinical investigators, monitoring reports, IRB documentation, CRFs, data collection, and study drug accountability. The inspectors also compared selected subject e-CRFs and were compared with the firm's data listings.

The inspection revealed that the applicant's new drug application did not contain all of the information required under 21 CFR 314.50. Specifically, the application did not contain all of the tabulations of the data from each adequate and well-controlled study under 21 CFR 314.126. We note that the applicant did not report that the following pain assessments were not performed in protocol R331333-PAI3003: At the site of Dr. Richard Pollak, 24 hour pain assessment for subject 304078, and at the site of Dr. Ira Gottlieb, 48-hour pain assessments for subjects 305069 and 305147 and 72-hour pain assessment for subject 305178. The review division may wish to evaluate the impact, if any, of these unreported assessments on the data acceptability.

The sponsor's monitoring procedures appear to have been conducted adequately, and the data submitted by sponsor may be used in support of the respective indication.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Pollak, Gottlieb, Beretta and Afilalo revealed no significant problems that would adversely impact data acceptability. The inspection of the sponsor revealed that the applicant's new drug application did not contain all of the information required under 21 CFR 314.50. Specifically, the application did not contain all of the tabulations of the data from each adequate and well-controlled study under 21 CFR 314.126, as detailed above. The review division may wish to evaluate the impact, if any, of these unreported assessments on the data acceptability. The data submitted from the inspected sites are acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Antoine El-Hage
9/12/2008 05:42:34 AM
PHARMACOLOGIST

Constance Lewin
9/12/2008 08:58:47 AM
MEDICAL OFFICER

Executive CAC

Date of Meeting: August 26, 2008

Committee: David Jacobson-Kram, Ph.D., ONDIO/PharmTox, Chair
Abby Jacobs, Ph.D., ONDIO/PharmTox, Member
Bayo Laniyonu, Ph.D., DMIHP, Alternate Member
Paul Brown, Ph.D., ONDIO/PharmTox, Member
Adam Wasserman, Ph.D., DAARP, Team Leader
Kathleen Young, Ph.D., DAARP, Presenting Reviewer

Author of Draft: Kathleen Young, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 22-304

Drug Name: Tapentadol

Sponsor: Ortho-McNeil Pharmaceutical, Inc.

Background: Tapentadol is a new molecular entity that is being developed for the oral treatment of moderate to severe, acute and chronic pain at doses of 100 mg up to 6 times/day (600 mg/day, and up to 700 mg on the first day of treatment). Tapentadol is active primarily through agonist activity at the mu- and sigma2 receptors, and also inhibits norepinephrine uptake.

The results of non-clinical pharmacology studies showed the analgesic potency of tapentadol to be 2X-3X that of morphine, although the affinity for the mu-opioid receptor was 1/50 the affinity of morphine.

Tapentadol was evaluated in a standard battery of genetic toxicity studies and found to be equivocal for clastogenicity. A positive response was found in one of two *in vitro* Chromosome Aberration studies in Chinese hamster V79 cells, showing increased incidence of structural chromosome aberrations at concentrations greater than 1000 mcg/ml in the presence of metabolic activation with S9. No evidence of genetic toxicity by tapentadol was found in the Ames test, the *in vivo* assay for clastogenicity in rat bone marrow cells, and in rat hepatocytes in the Unscheduled DNA Synthesis assay.

Mouse Carcinogenicity Study

A 2-year oral gavage study was conducted in CD-1 mice given tapentadol doses of 50 (LD), 100, (MD1) and 200 (MD2) mg/kg/day. The high dose group (HD) received the following treatments, with dose adjustments during the study: 200 mg/kg/day (Weeks 1-14), escalation to 300 mg/kg/day (Weeks 15-27) upon Agency recommendation, and subsequent reduction to 200 mg/kg/day (Weeks 29-91) following observations of increased mortality after the dose escalation. An additional, dose-escalation high dose

group (n=9/sex/group) was used to test tolerability of the high dose per Agency recommendations. The additional group was given 200 mg/kg/day during Weeks 1-13 and 300 mg/kg/day during Weeks 14-28, followed by dose reduction to 200 mg/kg/day during Weeks 29-91. Dosing was terminated in the MD2 (200 mg/kg/day) male mice during Week 100 and in the MD female mice during Week 99, due to excessive mortality (20 surviving animals). The high dose groups were terminated in Week 92, also due to low survival. The surviving mice were kept to the end of the 104-week period without treatment for histopathologic examination. All animals, including the mice found dead and sacrificed in extremis were examined microscopically. The doses were originally selected based on the results of a 13-week oral dose selection study and received prior Agency concurrence (see ExecCAC meeting of December 9, 2003).

The duration of treatment and survival in the 2-year study was adequate in all groups for valid statistical evaluation of the parameters examined. According to the Sponsor, there was a treatment-related increase in hepatocellular carcinomas in the high dose male mice (incidence 4/51 compared to 0 – 1 per group in the controls, low dose and mid dose mice), that was found not statistically significant by Agency statistical analyses for this common tumor type in mice. There were statistically significant trends for subcutis sarcoma in male mice. However, there were no statistically significant treatment-related increases in any dosed group compared to concurrent controls. Historical control data suggested that the tumor incidences are within the background for the strain in this laboratory.

Rat Carcinogenicity Study

A 2-year study was conducted in Wistar rats, at tapentadol oral doses of 10, 50, 125, and 250 mg/kg/day administered by admixture in the diet (n=50/sex/group). Two additional groups received negative control (pelleted standard rat maintenance diet). The doses were based on the results of a 13-week preliminary oral (dietary) toxicity study, and the protocol received ExecCAC concurrence (see minutes of ExecCAC meeting of January 22, 2002, IND 61,345).

Survival in the 2-year study was adequate in all groups at the end of the dosing period for valid statistical evaluation of the parameters examined. Agency statistical analyses detected positive trends in the incidence of hepatocellular adenoma in the female rats ($p < 0.025$) with incidence of 2% and 4% at 125 and 250 mg/kg/day, respectively. There was a statistically significant dose response for increased liver adenomas + carcinomas in the female rats, but no statistically significant increases over controls in any treated group. Historical control data suggested that the tumor incidences are within the background for the strain in this laboratory.

Executive CAC Recommendations and Conclusions:

2-Year Mouse:

The Committee concurred that the study was adequate and was negative for carcinogenicity.

2-Year Rat:

The Committee concurred that the study was adequate and was negative for carcinogenicity.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DAARP
/Adam Wasserman, Ph.D., Team leader, DAARP
/Kathleen Young, Ph.D., Reviewer, DAARP
/Matthew Sullivan, RPM, DAARP

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/s/

David Jacobson-Kram
9/2/2008 12:20:58 PM

Stradley, Sara

From: Stradley, Sara
Sent: Friday, August 01, 2008 11:07 AM
To: 'Dusek, Kathleen [PRDUS]'
Cc: Sullivan, Matthew; Stradley, Sara
Subject: RE: NDA 22-304 Information Request/July 30 and July 31 and Aug 1

Katie

We have one more information request for this week. Our clinical reviewer looked over the information you sent on July 31 and has the following request:

For the shift tables for labs, vital signs, and ECGs, please insert percentages for each value, calculated as percentage of total subjects in the treatment who have values for the lab/vital sign/ecg.

Thanks
Sara

From: Stradley, Sara
Sent: Thursday, July 31, 2008 4:06 PM
To: 'Dusek, Kathleen [PRDUS]'
Subject: FW: NDA 22-304 Information Request/July 30 and July 31

From: Stradley, Sara
Sent: Thursday, July 31, 2008 3:20 PM
To: Stradley, Sara; 'KDusek@prdus.jnj.com'
Cc: Sullivan, Matthew
Subject: RE: NDA 22-304 Information Request/July 30 and July 31

Hi

We have the following additional information requests:

Provide a listing of all subjects in the tapentadol IR development plan who discontinued treatment due to a lab abnormality. The subjects should be listed by safety analysis group. Include the lab abnormality resulting in discontinued treatment, and links to narratives and pertinent sections of study reports.

Provide a table of potentially important lab values by treatment group and dose received for tapentadol IR and placebo.

Thanks
Sara

From: Stradley, Sara
Sent: Wednesday, July 30, 2008 11:21 AM
To: 'KDusek@prdus.jnj.com'
Cc: Stradley, Sara; Sullivan, Matthew
Subject: NDA 22-304 Information Request/July 30

Hi Kathleen

I am covering for Matt while he is on vacation this week.

We have the following information requests for NDA 22-304 (Tapentadol). Please provide your response by Aug 8, 2008. Let me know if you have any questions.

1. Provide Shift Tables for ECGs by treatment for the complete phase 2/3 multiple dose double blind pooled

analysis set and the Phase 3 open label extension safety analysis set.

2. For the Phase 2/3 multiple dose, double blind analysis set, provide a table displaying the Mean Change At Endpoint Compared To Baseline for all laboratory tests performed, by dose of tapentadol, as shown below. Since this table shows changes, and not absolute lab values, all studies in the data set should be pooled, including KF5503/4 and KF5503/8.

Test name	Units	Placebo	0-30 mg	>30-60mg	>60-90mg	>90-120mg	Flexible Dose	All Tapentadol

Thanks

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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/s/

Sara Stradley
8/1/2008 11:13:25 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-304

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 08560-0200

3/31/08

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

Dear Ms. Dusek:

Please refer to your new drug application (NDA) dated January 22, 2008, received January 23, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for tapentadol HCl.

We also refer to your submissions dated March 4, 13, and 19, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 23, 2008.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients birth to ∞ years of age.

b(4)

NDA 22-304
Page 2

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

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/s/

Sharon Hertz
3/31/2008 02:23:41 PM
Signing for Bob Rappaport, M.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-304

NDA ACKNOWLEDGMENT

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 08560-0200

2/4/08

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 for the following:

Name of Drug Product: Tapentadol Hydrochloride

Date of Application: January 23, 2008

Date of Receipt: January 23, 2008

Our Reference Number: NDA 22-304

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 March 23, 2008, 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/oc/datacouncil/spl.html>. 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 be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above 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/cder/ddms/binders.htm>.

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

Sincerely,

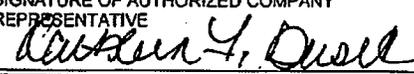
{See appended electronic signature page}

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

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/s/

Matthew Sullivan
2/4/2008 10:26:45 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS JOHNSON AND JOHNSON Kathleen Dusek 1125 Trenton-Harbourton Road PO Box 200 Titusville PA 08560 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-304			
2. TELEPHONE NUMBER 609-7302719		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
3. PRODUCT NAME none yet (tapentadol hydrochloride)		6. USER FEE I.D. NUMBER PD3007997			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes 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: <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td> <td>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.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Associate Director Global Regulatory Affairs DATE January 15, 2008			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,178,000.00					
Form FDA 3397 (03/07)					



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Pre NDA
Minutes

Food and Drug Administration
Rockville, MD 20857

IND 61,345

Johnson & Johnson Pharmaceutical Research & Development, LLC
1125 Trenton-Harbourton Road
Titusville, NJ 08560-02200

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

Dear Ms. Dusek:

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.

We also refer to the meeting between representatives of your firm and the FDA on June 5, 2007. The purpose of the meeting was to discuss your planned NDA submission for tapentadol hydrochloride immediate-release tablets.

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, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Sponsor Meeting Agenda

MEETING DATE/TIME: June 5, 2007/3:30 PM

LOCATION: 10903 New Hampshire Avenue, Bldg 22, Room 1313, Silver Spring, MD 20993

APPLICATION/DRUGNAME: IND 61,345/tapentadol HCl immediate-release

INDICATION: moderate to severe pain

SPONSOR: Johnson & Johnson Pharmaceutical Company

TYPE OF MEETING: Type B; Pre-NDA

MEETING CHAIR: Rob Shibuya, MD; Acting Clinical Team Leader

MEETING RECORDER: Lisa Basham, MS; Regulatory Project Manager

Name	Title
Bob Rappaport, MD	Director, DAARP
Sharon Hertz, MD	Deputy Division Director, DAARP
Rob Shibuya, MD	Acting Clinical Team Leader
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Adam Wasserman, PhD	Pharmacology/Toxicology Supervisor
Tom Permutt, PhD	Director, Division of Biometrics 2
Joan Buenconsejo, PhD	Biostatistics Reviewer
Atul Bhattaram, PhD	Pharmacometrics Reviewer
David J. Lee, PhD	Clinical Pharmacology Reviewer
Michael Klein, PhD	Acting Director, Controlled Substance Staff (CSS)
Lori A. Love, MD, PhD	Medical Officer, CSS
Denise Toyer, PharmD	Deputy Director, Division of Medication Errors and Technical Support (DMETS), Office of Surveillance and Epidemiology (OSE)
Lauren Lee, Pharm D	Safety Evaluator Team Leader, Division of Drug Risk Evaluation (DDRE), OSE
Gita Akhavan-Toyserkani, Pharm D, MBA	Safety Evaluator, DDRE, OSE
Matthew Sullivan	Regulatory Project Manager
Lisa Basham, MS	Regulatory Project Manager

J&JPRD	Title
Kathleen Dusek, RPh, RAC	Associate Director, Regulatory Affairs
Peggy Ferrone	Manager, Regulatory Affairs
Juergen Haeussler, MD, PhD	Vice President, Therapeutic Area Head Pain
David Hilfiker	Associate Director, Regulatory Affairs, Johnson & Johnson FDA Liaison Office
Bernhard Mangold, MD, PhD	Director, Clinical Pharmacology
Partha Nandy, PhD	Associate Director, Advanced Modeling and Simulation
Akiko Okamoto, ScD	Assistant Director, Clinical Biostatistics,
Pamela Povey, PhD	Director, Global Regulatory Affairs Leader
Christine Rauschkolb, MD, PhD	Senior Director, Compound Development Team Leader
Barry Schwab, PhD	Executive Director, Clinical Biostatistics
David Upmalis, MD	Senior Director, Clinical Team Leader
Charles Oh, MD	Associate Director, Clinical
GRT	
Burkhard Daldrup, PhD	Head of Corporate Regulatory and Safety Affairs
Tom Huijbers, MSc	Regulatory Affairs Manager
Anton Hoos, MD	Head of Development
Frank Laschewski, MD	Head Drug Safety Medical Evaluation
Jens-Uwe Stegmann, MD	Therapeutic Area Analgesics – Scientific Advisor
Horst Weber, MD	Global Head of Therapeutic Area Analgesics

Background: The sponsor submitted a meeting request dated March 5, 2007. The meeting was granted and scheduled for June 5, 2007. The supporting background package was submitted on April 27, 2007, received April 30, 2007. The Agency's responses to the sponsor's questions were forwarded to the sponsor on May 31, 2007. On June 4, 2007, the sponsor informed Lisa Basham that they intended to focus the discussion on questions 8, 9, 12, 17, 19, 23, 34, 35, 36, 37, and 40, however, all questions and Agency responses are listed below, in numerical order, for reference. Sponsor questions are in italicized text, Agency responses are in bolded text, and discussion during the meeting is in normal text.

Meeting Minutes

Quality/CMC Questions/Topics

Question 1. Does the Agency agree that the responses provided in the Sponsor's amendment to IND 61,345, Serial No. 165 (Attachment 2) relating to the use of [redacted] starting material are acceptable?

b(4)

Response:

The supportive information provided in regard to considering [redacted] starting material is acceptable. However, you need to provide long-term stability and test data for the proposed starting material as requested by the Agency. Additionally, the final proposed specifications for [redacted] should be included in the NDA together with maintenance of [redacted] starting material.

b(4)

DISCUSSION: No discussion necessary.

Question 2. Does the Agency agree with the proposal to provide 9 months of drug product registration stability data in the NDA, with the 12-month stability data provided within 4 months following submission?

Response:

The NDA may be submitted with 9-months of stability data and stability updates (12 months) may be submitted within 4 months following submission. However, expiration dating period will be granted based on available and satisfactory stability data. Therefore, you may only receive a [redacted] expiry initially. Note that, under the Good Review Management Practices, the reviews will have to be finalized by mid-cycle. While every effort will be made to review the stability updates, their review will depend on the timeliness of the submission, the extent of submitted data, and the available resources.

b(4)

DISCUSSION: No discussion necessary.

Nonclinical Questions/Topics

Question 3. Does the Agency agree that the proposed content of the nonclinical sections of the tapentadol IR NDA are sufficient to support filing and potential approval of the NDA?

Response:

The Division agrees that the list of nonclinical studies, including your reproductive toxicology studies referenced in your submission N190 (general correspondence), completed to date would appear to support filing of an NDA application. Final determination of the adequacy of the submitted studies, however, cannot be determined until review of your NDA submission.

DISCUSSION: No discussion necessary.

Question 4. Does the Agency agree with the proposal to submit tumor data from each rodent carcinogenicity study as an electronic dataset in SAS Transport (XPORT) file format created in Version 5 of SAS software?

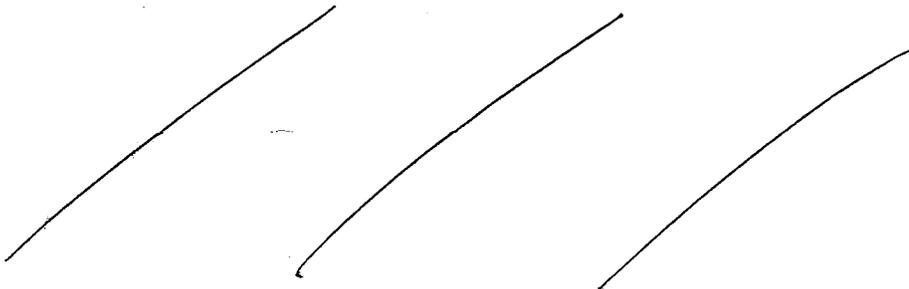
Response: Yes.

DISCUSSION: No discussion necessary.

Question 5. Does the Agency agree with this proposed definition of the element "duration" in the Study Tagging File (STF)?

Response: As the rodent carcinogenicity study results submitted in SAS Transport file format contain data from two-year studies, it is not clear why separate designations for short, medium, or long studies are necessary. Please clarify your request for further input.

DISCUSSION: No discussion necessary.



b(4)

Drug Products that is available at the following web page:
<http://www.fda.gov/guidance/index.htm>.

Additional Nonclinical Comments:

- For the NDA submission, any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for the NDA submission (ICHQ3A, ICHQ3B(R)).
 - Adequate qualification should include:
 - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication.
 - Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 µg/day should be set for genotoxic or potentially genotoxic residual intermediates in the synthetic scheme unless otherwise justified.
 - Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:
 - Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication.
 - Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT 1.5 µg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
- NOTE: A Guidance to Industry regarding setting acceptable specifications for potential genotoxic impurities is in development in CDER OND. The specifications above represent our current thinking on this topic at this time.**
- The Division recommends that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.
- The NDA submission should contain information on potential leachables and extractables from the drug container closure system. Provide a toxicological

evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled specified route of administration. The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

DISCUSSION: No discussion necessary.

Clinical Pharmacology Questions/Topics

General Questions

Question 7. 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 IR NDA?

Response: The types of clinical pharmacology studies conducted appear adequate.

DISCUSSION: No discussion necessary.

Questions Related to Modeling and Simulation

Question 8. Does the Agency agree with the proposed population PK/PD/AE analysis for tapentadol IR?

Response: We agree with the proposed PK/PD/AE analysis for tapentadol IR. We also recommend that you consider analyzing data from studies other than KF5503/21, PAI-2003/KF5503/22 and PAI-3003. In certain instances a patient might have an event multiple times. Submit these data as well.

DISCUSSION: The sponsor inquired as to which other studies they should include in the PK/PD/AE analysis. They noted that they have data from study KF21 and KF22 (Phase 2 bunionectomy studies) and study PAI-3002 (Phase 3 bunionectomy study). Dr. Bhattaram indicated that these studies should be adequate.

Question 9. Does the Agency agree with the proposal to use data from Phase 3 study KF5503/32 (R33-333-PAI-3003) for the population exposure-efficacy (PK/PD) analysis?

Response: We strongly recommend that you consider conducting exposure-efficacy analysis for data collected from Phase 2 studies.

DISCUSSION: The sponsor stated that they plan to analyze the efficacy data from Phase 2 studies by study. Dr. Bhattaram responded that this is acceptable.

Question 10. Does the Agency agree with the proposal to pool the Phase 2 and 3 studies for the population exposure-safety (PK/AE) analysis?

Response: Yes, the proposal to pool Phase 2 and Phase 3 studies for PK/AE analysis is acceptable.

DISCUSSION: No discussion necessary.

Question 11. Does the Agency agree with nausea and vomiting as the proposed primary safety variables for the population PK/AE analysis?

Response: We strongly recommend that you include additional safety variables which show strong trends that are associated with the CG 5503 treatment group. In addition to the time to event (First Event) analysis as proposed, you should also consider analysis strategies that would explain repeated events in each subject.

Discussion: No discussion required.

Question 12. Does the Agency agree with SPID₄₈ as the proposed primary efficacy variable and with the proposed imputation method for missing values of the PD variable for the population PK/PD analysis?

Response: The population PK/PD analysis must be performed using a similar endpoint and imputation scheme as that used for drug approval. The method of imputation is unacceptable (see our response to Question 15). In addition, we strongly recommend that you consider repeated measures analysis for the pain scores collected in each individual, instead of using a metric that would describe the area under the curve.

DISCUSSION: The sponsor indicated that they wish to discuss the imputation issue under question 19. Regarding the second point, they agreed to perform repeated measures analysis for the pain scores collected in each individual and added that they will perform this analysis by study.

Question 13. Does the Agency agree that dose-response analysis of the tapentadol and oxycodone data from the two Phase 3 studies as described in Section 6.3.2.4 using the planned Modeling will

_____ the product label (see Section 6.4.4.2 of this document)?

Response: Yes, the approach is acceptable. However, whether it would _____ in the label will be a review issue.

DISCUSSION: No discussion necessary.

Question 14. Is the proposed format for the NONMEM datasets acceptable to the Agency?

Response: Please find details on the format for the NONMEM datasets:

Please submit the following datasets to support the population analysis:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a 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.

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.

DISCUSSION: No discussion necessary.

Clinical/Statistical Questions/Topics

Question 15. Does the Agency agree that study KF5503/33 (R331333-PAI-3002) will be accepted as a pivotal study for the approval of the tapentadol IR NDA?

Response: The study population and primary endpoint are acceptable.

DISCUSSION: No discussion necessary.

Question 16. The Sponsor contends that filing with successful studies for KF5503/32 (R331333-PAI-3003) Bunionectomy and KF5503/33 (R331333-PAI-3002) End-Stage Joint Disease will support approval for filing the tapentadol IR NDA for the relief of moderate to severe pain _____ Does the Agency agree?

Response: These studies appear to be sufficient to support filing an application for the indication of a moderate to severe acute pain.

DISCUSSION: No discussion necessary.

Question 17. Is the proposed content of the Summary of Clinical Efficacy (Module 2.7.3) acceptable to the Agency?

Response:

- Yes
- In studies where “reload” was permitted, we would like to see descriptive statistics comparing the two groups for safety and efficacy.

DISCUSSION: The sponsor stated that this issue applies to one Phase 3 bunionectomy study, along with the Phase 2 bunionectomy study. For the Phase 3 study, they propose to define the reloading group as those who received a second dose within three hours of the first dose. This group would be evaluated using a subset analysis. The remainder would be defined as the remaining dose group. Dr. Shibuya found the definition for the reloading group acceptable.

Question 18. Does the Agency agree with the proposal to present the efficacy results of the two Phase 3 pivotal studies separately within the integrated summary of efficacy (ISE), as opposed to pooled across studies?

Response: Yes

DISCUSSION: No discussion necessary.

Question 19. Does the Agency agree that the proposed Statistical Analysis Plan (SAP) for the Phase 3 studies will adequately characterize the efficacy profile of tapentadol IR?

Response: With the exception of the concerns expressed below, the proposed analyses appear adequate to allow for an evaluation of efficacy.

- As stated in the Type C meeting on December 16, 2005, LOCF is not adequate as the method for imputing missing data in the primary efficacy analysis in a setting where dropouts may be nonrandom and the reason for dropping out may be associated with treatment assignment. You should use a conservative strategy, such as the suggested sensitivity analysis (i.e. BOCF), to impute missing data in the primary analysis.

DISCUSSION: The sponsor acknowledged the need for performing the BOCF imputation method, however, they wish to retain LOCF as the primary endpoint for the following reasons. All published literature utilizes LOCF imputation and they wish to compare their results to those from published literature. Furthermore, the EMEA recommends LOCF as the appropriate imputation method and they plan to apply for registration in other countries. Last, the sponsor based the sample size calculation using LOCF to impute missing data. Dr. Hertz acknowledged the sponsor's comments but requested that the minutes clearly state that the sponsor understands

and agrees that for the U.S. application, a positive study using LOCF that fails more conservative imputation methods will not be considered an adequate demonstration of efficacy and will not support approval. The sponsor acknowledged their understanding.

- **In the Discontinuation/Completion Section, you have included “other” as one of the categories under reason for discontinuation. “Other” may potentially mask an adverse event that has not been captured. Thus, you should thoroughly collect and document as much information as possible for discontinuations to alleviate concerns regarding treatment-related dropouts.**

DISCUSSION: The sponsor stated that they will use every effort to minimize the number of patients falling into the “other” category.



b(4)



POST MEETING NOTE:

We are undertaking further internal review and will forward further recommendations as soon as possible.

Question 20. Does the Agency agree with the proposal to provide only one document as a summary of integrated efficacy in both Modules 2.7.3 and 5, with the supporting statistical output to be provided under Module 5?

Response:

- Yes. In addition, see the additional comments at the end of this document.

DISCUSSION: No discussion necessary.

Question 21. Does the Agency concur that the proposed clinical studies support the proposed indication of "<Trade Name> (tapentadol) IR tablets are indicated for the relief of moderate to severe pain"

b(4)

Response: It is premature for us to comment on the wording of the indication prior to review of the data. However we note that the wording of this indication could imply that the product is appropriate for management of chronic pain, and so should include the word "acute" to reflect the data proposed for the application.

DISCUSSION: No discussion necessary.

Question 22. Does the Agency concur that the proposed clinical studies, as designed, support the proposed Dosing and Administration recommendation?

Response:

- It is premature to comment on labeling in this detail at this time. It is possible that the language in the acute pain section may be supported by the study designs. However, it is unclear what data you will use to support the _____ We recommend that you submit an annotated label that clearly documents the support for each element of this section.

b(4)

b(4)

DISCUSSION: No discussion necessary.

Question 23. Is the proposed content of the Summary of Clinical Safety (SCS) (Module 2.7.4) acceptable to the Agency?

Response: You must provide a summary of safety from the studies of the ER formulation.

DISCUSSION: The sponsor stated that, at the time of filing, the Phase 3 studies for the extended-release formulation will be ongoing and blinded. Rather than submit data from those studies, they proposed to submit data from the completed Phase 2 studies and to present these data separately, by study (4 studies). Dr. Hertz responded that the sponsor should submit deaths and SAEs from the Phase 3 studies even though the studies will still be blinded. She encouraged the sponsor to submit data in one table, including summary data from all pertinent trials, acknowledging that there will be empty cells.

Question 24. Does the Agency agree that the proposed SAP for integrated safety will adequately characterize the safety profile of tapentadol IR?

Response: The proposed plan appears appropriate although additional analyses may be requested during the review.

DISCUSSION: No discussion necessary.

Question 25. Does the Agency agree with the proposal to integrate safety data and to present the results of the Phase 2 and 3 studies using the IR formulations in the Clinical Summary of Safety?

Response: Yes

DISCUSSION: No discussion necessary.

Question 26. Does the Agency agree with the proposal to integrate only selected Phase 1 studies and to pool selected safety data from within these Phase 1 studies for the IR formulation?

Response: Yes

DISCUSSION: No discussion necessary.

Question 27. Does the Agency agree with the proposed strategy for updating the Medical Dictionary for Regulatory Activities (MedDRA) codes for the integrated safety data set?

Response: Yes. In addition, include the verbatim terms in your safety database.

DISCUSSION: No discussion necessary.

Question 28. Does the Agency agree with the proposal to provide only one document as a summary of integrated safety in both Modules 2.7.4 and 5, with the supporting statistical output to be provided under Module 5?

Response: Section 2.7.4 is intended for a summary, and hence, is limited in size. The ISS is actually not a summary as much as it is an analysis across studies, and Section 5.3.5.3 has no size restriction and is intended for such analyses. Our preference is that the ISS be located in 5.3.5.3.

DISCUSSION: No discussion necessary.

Question 29. Does the Agency agree with the proposal for inclusion of patient narratives and case report forms (CRFs)?

Response: Yes

DISCUSSION: No discussion necessary.

Question 30. 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 IR formulation?

Response: Yes

DISCUSSION: No discussion necessary.

Question 31. Does the Agency agree with the proposed formatting and naming conventions for the SAS transport files?

Response: The proposed formatting and naming conventions appear acceptable. In addition, provide data definitions (define.pdf or define.xml) for all variables.

DISCUSSION: No discussion necessary.

Question 32. Does the Agency agree that the Sponsor's proposed general safety analysis is sufficient to support the proposed label information for Indication (see section 6.4.4.1) and Dosage and Administration (see section 6.4.4.2)?

Response:

- The proposed safety analysis could support an acute pain indication.

- As noted, the Dosage & Administration section _____ which is not supported by the currently proposed submission.

b(4)

DISCUSSION: No discussion necessary.

Question 33. The Sponsor contends that the planned safety exposure as discussed in Section 6.4.8 is sufficient to support the review and approval of the tapentadol IR NDA for an indication in moderate to severe pain. Does the Agency agree?

Response:

- As this is an NME it is extremely important that we evaluate all available information.
- You have additional data from the ER formulation studies; safety data from these studies must be submitted with this NDA.
- Unless unforeseen safety issues are identified, the proposed database may support an acute pain indication.

DISCUSSION: No discussion necessary.

Regulatory Questions/Topics

Question 34. Does the Agency agree with the proposed content for the safety update report for the tapentadol IR NDA?

Response: Yes, provided that updated information for the ER formulation is also updated.

DISCUSSION: C

will, however, include safety data from the ER formulation for SAEs and deaths.

They

b(4)

Question 35. Does the Agency agree that the performed studies are sufficient to adequately address questions from both the Division and Controlled Substances Staff for this new molecular entity opioid?

Response:

- Provide a proposal for scheduling tapentadol in an appropriate schedule of the Controlled Substances Act (CSA) with justification.

- **Provide all information and data related to the abuse liability assessment, including diversions and overdose potential, as outlined above. Specifically, the following should be included:**
 - **Details on the human abuse liability study (HP5503/14 R33133-PAI-1107) including the protocols, raw data, and all adverse events.**
 - **Details (protocols and raw data) on dose escalation/dose ranging studies (HP5503/13 R33133-PAI-1005 and HP 5503/03), including all adverse events occurring during the studies.**
 - **Details of Phase 3 studies, including protocols, raw data and adverse events.**
 - **Descriptions of all reports of abuse, overuse, or overdose, or drug that is lost, missing or unaccounted for in the clinical trials.**
 - **Descriptions from clinical trial data of all reports related to drug withdrawal and withdrawal symptoms and any other indication of dependence in humans.**
 - **Details on the animal abuse liability and drug dependence studies, including the protocols and raw data.**
- **In addition to the above, we recommend that you address the following:**
 - **For MedDRA coding of adverse events, provide the coding convention as MedDRA SOC terms may not capture unusual signs and symptoms that may be related to abuse liability that could be included in the verbatim descriptions of adverse events (AEs).**
 - **Please be consistent in providing “normalized” doses of tapentadol, expressed as either the free base or hydrochloride salt, across all studies for comparison of data.**

DISCUSSION: The sponsor indicated their acceptance of all requests. Regarding the comment requesting normalized doses, they noted that some Phase 2 studies were reported using the base and some using the salt. They proposed providing a summary document for these studies and noted that the Phase 3 studies were reported using the base doses. They will provide a table defining the conversion of base to salt and clearly distinguish which studies used which form of the drug.

The sponsor inquired about the scheduling process and whether there is a way to minimize the time between approval and scheduling. They asked whether it is possible to publish the proposed rule prior to approval. Dr. Klein responded that the DEA publishes the proposed rule and will not do so until an FDA approval action occurs. He added that the further delay can be minimized if the company and the Agency agree on scheduling. The sponsor offered to provide their 8-factor analysis to the Agency for concurrence. Dr. Klein stated that it is unnecessary for the sponsor to perform the analysis because the Agency will perform their own. CSS relies on analysis of data from preclinical, clinical, and drug abuse studies as well as all other relevant data provided in the NDA submission. He added that the Agency will do everything that they can to

minimize potential delay in a final scheduling action, by ensuring that appropriate paperwork is provided to the Assistant Secretary for Health (HHS) and the DEA in a timely manner.

Question 36. Does the Agency agree with the proposed RiskMAP outline for tapentadol IR?

Response: The immediate-release formulation of tapentadol, if used for an acute pain indication, would benefit from a careful pharmacovigilance program. [] b(4)

We also note the draft proposal does not include detailed information about surveillance and intervention components to monitor for appropriate use and abuse, which are important elements of many of the current risk management programs for opioids. Please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, submit this information with the NDA/BLA application.
- We encourage you to submit the proprietary name and all associated labels and labeling for review as soon as available.

DISCUSSION: The applicant stated that they plan on conducting a pharmacovigilance program for the IR formulation [] They asked for confirmation that the IR formulation will not require a RiskMAP. Dr. Hertz acknowledged that the IR formulation will not require a RiskMAP, and added that RiskMAPs are not currently being required for IR formulations unless there is something unusual about them, e.g., a particularly vulnerable population, a more highly abusable dosage form, etc. [] b(4)

Question 37. Does the Agency agree a partial waiver for tapentadol IR for the 0-2 year old pediatric population can be granted?

Response: No. Approved opioids have proven use in the pediatric population down to age 0. As such, an age-appropriate formulation of tapentadol could be developed and tested in young pediatric patients.

DISCUSSION: The applicant noted their understanding that a deferral would be granted for the

[REDACTED]

b(4)

Question 38. Does the Agency agree that a deferral for studies in pediatric populations, aged 2-18, can be granted for tapentadol IR?

Response: Yes

DISCUSSION: No discussion necessary.

Question 39. Does the Agency believe that the tapentadol IR NDA will be the subject of discussion by an FDA Advisory Committee Meeting based on the available data presented in this briefing package?

Response: At this time, we have no plans that an Advisory Committee would be convened to discuss tapentadol.

DISCUSSION: No discussion necessary.

Question 40. The Sponsor would like to know the Agency's current thinking regarding the use of

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Response:

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Additional CMC comments

Provide the following CMC information in the proposed NDA:

- **The limits for impurities and degradation products in the drug substance and drug product should conform to ICH Q3A “Impurities in New Drug Substances,” dated February 11, 2003) and Q3B “Impurities in New Drug Products” dated November 14, 2003) guidelines.**
- **Degradants must be monitored and reported when above 0.05%, identified when possible when above 0.10%, and qualified when consistently above 0.15%.**
- **Impurities exceeding 0.15% in the drug substance should be supported by safety studies.**
- **A well documented Pharmaceutical Development Report as per ICH Q8 guideline detailing critical attributes and parameters involved in the development of the drug and leading to the final manufacturing/formulation processes.**
- **CFN numbers, names, addresses, functions and contact persons of the all the sites involved in manufacturing, testing, packaging and labeling of the drug substance and the drug product**
- **A statement that all of the above sites are ready for inspection**
- **Appropriate amount of stability data to cover the proposed expiration dating**

Additional FDA Comments

A. The division requests the following for the submitted datasets:

1. **The integrated safety dataset that should include the following fields/variables:**
 - **A unique patient identifier**
 - **Study/protocol number**
 - **Patient’s treatment assignment**
 - **Demographic characteristics, including gender, chronological age (not date of birth), and race**
 - **Dosing at time of adverse event**
 - **Dosing prior to event (if different)**
 - **Duration of event (or start and stop dates)**
 - **Days on study drug at time of event**
 - **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
 - **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).**
 - **Marker for serious adverse events**

- Verbatim term
2. The adverse event dataset should 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 should also include the Verbatim term taken from the case report form.
 3. Please 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 should appear and does not address other content that is usually contained in the adverse event data set.
 4. In the adverse event data set, please 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. Please 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. Please 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, please 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.

DISCUSSION: Because the SMQ method of analysis is new to the applicant and they have not yet assessed the difficulty in performing it, they inquired as to whether they can submit this analysis in the 120-day safety update. Dr. Hertz provided a tentative agreement, but stated that this will be further considered and commented upon in a post meeting note.

POST MEETING NOTE:

Upon further internal review, it was noted that these analyses of the safety data are what help us see signals in the AEs. Therefore, it would not be appropriate to delay submission until the 120-day safety update. These analyses are considered a basic part of the NDA which must be complete at time of submission.

8. The spelling and capitalization of MedDRA terms should 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 should 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 should be in numeric format.
 11. Please 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 should be formatted as ISO date format.
 13. Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should 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 should be included in the datasets.
 14. All datasets should contain the following variables/fields (in the same format and coding):
 - Each subject should have one unique ID across the entire NDA
 - Study number
 - Treatment assignment
 - Demographic characteristics (age, race, gender, etc.)
- B. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should 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.
- C. 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.

KEY DISCUSSION POINTS:

1. The applicant is planning to analyze the efficacy data from Phase 2 by study.
2. The reloading group will be defined as those patients who receive a second dose within three hours of the first dose. A subset analysis will be performed on this subset of patients.
3. The applicant plans to retain LOCF as their primary endpoint.
4. The applicant understands that a positive study by LOCF that fails more conservative imputation methods will not be considered an adequate demonstration of efficacy for approval.
5. Relative potency to another drug must be demonstrated through convincing data.
POST MEETING NOTE: We are undertaking further internal review and will forward further recommendations as soon as possible.
6. At filing, the Phase 3 studies for the ER formulation will be ongoing and blinded. The applicant will provide safety data in the form of deaths and SAEs from these studies in a tabular format for ease of comparison.
7. The applicant will provide summary information regarding the form of drug used in various studies, i.e., base versus salt, and will provide information on how to convert the drug form for comparison between the studies. The Phase 3 studies were all conducted using the base form.
8. The DEA will not publish a proposed rule prior to an FDA action. The Agency will attempt to minimize delay by providing the necessary information to the DEA in a timely manner. The Agency will perform its own 8-point analysis.
9. A RiskMAP is not required for the IR formulation unless it is expected to have a specific risk associated with it that would merit one. Furthermore, the scheduling determination will influence the need for a RiskMAP.
10. Pediatric studies for both the over 2 and under 2 age groups is merited.
11. Under PREA, the applicant will be expected to develop an age-appropriate formulation for the 0-2 age group. Evaluation of this dosage form in neonates will be deferred until data in adults are obtained. If adequate safety data are obtained, a pharmacokinetic study may be all that is required.
12. Analgesia in neonates is considered an unmet medical need.
13.

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15. The applicant wishes to include the SMQ analysis in the 120-day safety update.
POST MEETING NOTE: Upon further internal review, it was noted that these analyses of the safety data are what help us see signals in the AEs. Therefore, it would not be appropriate to delay submission until the 120-day safety update. These analyses are considered a basic part of the NDA which must be complete at time of submission

**APPEARS THIS WAY
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Please note that the HLT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level 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		

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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.**

/s/

Lisa Basham
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DEPARTMENT OF HEALTH & HUMAN
SERVICES

EOP2
Minutes

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

EOP2
(Pharm/Tox)
Minutes

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,345

Grunenthal GmbH
c/o Grunenthal USA Inc.
Crossroads Business Center
One Pluckemin Way
Bedminster, NJ 07921

Attention: Keith Ryan
Director, Regulatory Affairs

Dear Mr. Ryan:

Please refer to your Investigational New Drug Application (IND) submitted under 505(i) of the Federal Food, Drug, and Cosmetic Act for CG5503.

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2005. The purpose of the meeting was to discuss your preclinical 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) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham-Cruz, MS
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 13, 2005
TIME: 11:30 AM
LOCATION: Teleconference
APPLICATION: IND 61,345
DRUG NAME: CG5503
TYPE OF MEETING: EOP2 Pharmacology/Toxicology

MEETING RECORDER: Lisa Basham-Cruz

FDA ATTENDEES:

Dan Mellon, PhD; Supervisory Pharmacologist
Lisa Basham-Cruz, MS; Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

sponsor (Grünenthal GmbH)

Dr. Ulrich Jahnel	Head Preclinical Drug Development
Dr. Rolf Terlinden	Pharmacokinetics Expert
Dr. Jörg Kolb	Head Preclinical Drug Safety
Dr. Johannes Schneider	Head Safety Pharmacology
Dr. Bettina Doepner	Global Regulatory Affairs
Ms. Regina Kleinert	International Project Manager
Mr. Keith Ryan	Director Regulatory Affairs, Grünenthal USA, Inc.

Guests(J&JPRD)

Dr. Timothy Coogan	Director, Global Preclinical Development
Dr. Johann Monbaliu	Research Fellow, Global Preclinical Development
Dr. Graham Bailey	Reproductive Toxicology
Dr. Ravi Desiraju	Vice President, Compound Development Team Leader
Dr. Sujata Manam	Director, Global Regulatory Affairs
Ms. Kathleen Dusek	Associate Director, Regulatory Affairs
Mr. Michael Kaufmann	Director, Regulatory Affairs, Johnson & Johnson FDA Liaison Office
Dr. David Upmalis*	Senior Director, Clinical Team Leader
Dr. Christine Rauschkolb*	Senior Director, Clinical Team Leader
Dr. Shaun Comfort*	Associate Director, Project Physician

* clinical attendees for observation only

BACKGROUND:

The sponsor submitted a meeting request, dated November 4, 2005, to discuss their preclinical program for CG5503. The meeting package, dated November 10, 2005, was received on November 14, 2005. The questions, included in the briefing package are shown below in italicized text. The Division's responses, forwarded to the sponsor prior to the meeting, are shown below in bolded text. During the telecon, the discussion (shown in normal text) pertained to the Division's response to numbers 2 and 4. The sponsor agreed to all other comments.

1. *The sponsor believes that the non-clinical toxicology program completed and summarized in this background document supports the proposed CG5503 acute Phase III programs. Does the Agency agree?*

Agency Response: The nonclinical toxicology program supports the entry into Phase 3 clinical trials. Segment III reproductive toxicology studies must be completed prior to entry of women of child-bearing potential not on birth control into clinical studies.

2. *In addition to the completed non-clinical toxicology program as summarized, a pre/postnatal study in rats is planned. The sponsor feels that this program supports the proposed NDA filing. (please refer to Question 4 and 5 below). Does the Agency agree?*

Agency Response: In general, the nonclinical toxicology program described supports the filing of the NDA; however the maternal exposure to the glucuronide-conjugate of CG5503 in reproductive toxicology studies must be sufficient to cover the expected maternal exposure in the pregnant female. Exposure to the glucuronide conjugate is of concern with the demonstration that the metabolite is pro-convulsant and appears to cross the blood-brain-barrier. Therefore, should the parenteral routes fail to provide the exposure coverage for this metabolite, reproductive toxicology studies using oral administration of CG5503 or the direct administration of the glucuronide-conjugate will be necessary to assess potential toxicity and establish a safety margin for human use unless an adequate justification is provided.

3. *Grunenthal considers the genotoxicity assessment to be complete and negative. Does the Agency agree?*

Agency Response: The genotoxicity studies conducted appear to be sufficient to inform the label. The final wording of the label will be determined upon review of the NDA.

4. *Based on the exposure achieved in the rat developmental toxicity study (Segment II) with subcutaneous administration, subcutaneous application of CG5503 in the planned pre/postnatal (Segment III) toxicity trial in the rat (2 x 5 mg/kg) is considered to be the most appropriate route of administration. Does the Agency agree with this proposal?*

Agency response: As stated previously, the subcutaneous route for the proposed Segment III study appears appropriate to achieve the plasma exposure necessary to cover the parent compound but exposure to the glucuronide metabolite will also need to exceed human exposure through this route or an oral Segment III study will need to be conducted in order to provide coverage for human exposure.

5. *We see no value in repeating the 26-week rat study to correct the design issues as the outcome would be similar. We view this study as completing the requirement for a*

chronic rodent toxicology study to support registration for the acute development programs. Does the Agency agree?

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Agency response: The design of the 26-week study, while not ideal, is considered acceptable and will satisfy Agency requirements for submission of a chronic study in the rodent.

6. *Based on the mortality in group 5, the additional high dosage group, we would recommend terminating the dose group. Does the Agency agree with this decision?*

Agency Response: You may terminate Group 5 rodents in the mouse carcinogenicity study.

MEETING MINUTES:

Following introductions, the discussion moved to the questions posed by the sponsor. The sponsor needed no further clarification on responses to questions 1, 3, 5, and 6. They wished to further discuss our responses to questions 2 and 4 regarding the metabolite glucuronide.

The sponsor indicated that they understood the Division's concerns regarding the lack of coverage for the glucuronide metabolite. The sponsor stated that to date they have conducted four Segment II studies, two IV and two SC. They do have data on the glucuronide metabolite levels in these studies and indicated that in terms of C_{max} they believe they have approximately 0.8 to 1.55 times the clinical levels. In terms of AUC, they have 0.4 to 0.5 times the coverage. They noted that these levels were less than anticipated.

The sponsor proposed a tiered approach to address the lack of adequate coverage through the data obtained in Segment III studies, where they propose to enhance the levels of both the parent as well as the glucuronide metabolite and ultimately exceed the exposures previously obtained in the Segment II studies. Their proposed approach is to conduct an enhanced Segment III study that would evaluate the effects of both the parent and glucuronide metabolite and, based upon those results, conduct a second Segment III study only if necessary. They noted that the initial dosing period for the Segment II study (Day 6-17) is the same as that for Segment III, i.e. from implantation (Day 6) to day 21 (weaning). In the enhanced Segment III study, they plan to look at litter size for evidence of numerical abnormalities and gross abnormalities, to separate and examine any abnormal pups, and also to compare growth during lactation. The pups would be tested for standard Segment III behavioral and fertility parameters. At weaning, they plan to sacrifice the dams and upon necropsy record the implantation scar count, which would indicate the *in utero* survival index. If there are any problems noted during these preliminary evaluations from pregnancy to weaning, the sponsor would complete a second Segment III study with the glucuronide metabolite via the oral route of administration.

Dr. Mellon expressed a concern that certain *in utero* abnormalities, e.g., rib development, would not be apparent during these gross morphological evaluations. The sponsor responded that normally, any significant changes would manifest as gross morphological changes that affect survivability. Dr. Mellon inquired whether the sponsor plans to evaluate delays in bone

maturation. The sponsor responded negatively. These abnormalities, they continued, would not be apparent except possibly in terms of body weight changes. Dr. Mellon inquired whether the sponsor plans to dose with the glucuronide metabolite. The sponsor responded that they plan to administer increasing doses of parent drug to increase the dose of both the parent and the metabolite. Potentially, they may have to perform two studies, with increasing oral doses of parent or metabolite, but would prefer to develop a paradigm (e.g. BID dosing) to enhance exposure to both in one study. Dr. Mellon stated that the tiered approach may be acceptable if the sponsor clearly addresses what would not be covered using this approach. He then asked if they have evidence that the glucuronide metabolite crosses the placental barrier. The sponsor stated that they do not have clear data on this issue. Dr. Mellon then asked whether glucuronide crosses the blood/brain barrier. The sponsor stated that they can detect a fraction of the metabolite in the brain. Dr. Mellon told the sponsor that their proposed tiered approach would appear to be acceptable; however, he requested that they submit their plan and rationale to the Division for review. He also noted that the determination if whether the proposed studies would provide adequate coverage for the parent compound and the glucuronide metabolite will have to be determined following analysis of the study results and corresponding toxicokinetic data. Exactly how the data will ultimately be presented in the label will be determined during review of the NDA.

ACTION ITEMS:

The sponsor will submit the tiered Segment III protocol for review.

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/s/

Lisa Basham-Cruz
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