CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

There is one patent, United States Patent # 6,607,748, that applies to the drug product Tramadol OAD tablets. Information on this formulation patent is being submitted with this NDA for future listing in the Orange Book. Attached is FDA Form 3542a (Patent Information) for Patent 6,607,748.

The reference listed product, Ultram® (NDA 02-281), has one unexpired patent, Patent 6,339,105, listed in the Orange Book.

Patent 6,339,105 is a method of use patent that describes a regimen for the administration of tramadol for the treatment of analgesia. The regimen involves a slower initial titration rate of tramadol. The proposed labeling for Tramadol Contramid® OAD will not contain any reference to this patented titration procedure.

Therefore, as per the FD&C Act 505(b)(2)(B), this method of use patent does not claim a use for which the applicant is seeking approval.

Department of Health and Human Services
Food and Drug Administration

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

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER: 21-745

NAME OF APPLICANT / NDA HOLDER: Labopharm Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Tramadol Contramid OAD

ACTIVE INGREDIENT(S): tramadol hydrochloride

STRENGTH(S): 100 mg, 200 mg and 300 mg

DOSAGE FORM: controlled release tablet

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	b. Issue Date of Patent	c. Expiration Date of Patent
6,607,748 B1	8/19/2003	6/29/2020

d. Name of Patent Owner	Address *(of Patent Owner)*	
Labopharm Inc.	480 Armand-Frappier Blvd	
	City/State: Laval, Quebec	
	ZIP Code: H7V 4B4	FAX Number *(if available)*: 450-686-9201
	Telephone Number: 450-686-0207	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Becky Prokipcak, CanReg Inc.	450 North Lakeshore Drive	
	City/State: Mundelein IL	
	ZIP Code: 60060	FAX Number *(if available)*: 847-837-8825
	Telephone Number: 1-866-722-6737	E-Mail Address *(if available)*: bprokipcak@canreginc.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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.)*	

5. No Relevant Patents

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

6. Declaration Certification

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

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

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

Date Signed: 9th November, 2005.

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(e)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: James Howard-Tripp	
Address: 480 Armand-Frappier Boul.	City/State: Laval, Quebec
ZIP Code: H7V 4B4	Telephone Number: 1-888-686-1017
FAX Number *(if available)*: 450-686-9201	E-Mail Address *(if available)*: jht@labopharm.com

ORTHO-McNEIL

Ortho-McNeil Pharmaceutical, Inc
1000 Route 202, PO Box 300
Raritan, New Jersey 08869-0602

908 218-6000 Telephone

November 9, 2005

Bob A. Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-550)
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: IND 64,317 (tramadol hydrochloride OAD (to be submitted as NDA 21-745))

Dear Dr. Rappaport:

Ortho-McNeil, Inc. ("OMI"), as agent of Biovail Laboratories International SRL ("Biovail"), hereby authorizes FDA to grant final approval of the Labopharm Product (which is now the subject of IND 64,317 and to be submitted as NDA 21-745), notwithstanding the three-year non-patent exclusivity awarded to NDA 21-692 for tramadol HCl extended release tablets under 21 U.S.C. 355(c)(3)(E)(iii). This authorization does not constitute a waiver of the rights under said exclusivity provision with respect to any other party or any other application for approval of tramadol HCl extended release formulations, which rights continue in effect until September 8, 2008. No rights are being waived by this letter with respect to the requirements for the submission of certifications to patents listed in connection with NDA 21-692. This waiver is permanent, and irrevocable, and exclusive (except for use in NDA(s) owned or controlled by OMI and Biovail).

Sincerely,

Ortho-McNeil, Inc.

Name: Jeffrey Smith
Title: President
Ortho-McNeil, Inc.

Acknowledged and agreed to by:
Biovail Laboratories International SRL

Name: Eugene Melnyk
Title: Executive Chairman of the Board
Biovail Laboratories International SRL

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

/s/

Paul Balcer
9/28/2006 01:23:21 PM
CSO

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-745 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 28 November 2005 **PDUFA Goal Date:** 28 September 2006

HFD 170 (DAARP) **Trade and generic names/dosage form:** Tramadol Contramid OAD (tramadol hydrochloride extended release) 100, 200 and 300 mg tablet

Applicant: Labopharm Canada, Inc. **Therapeutic Class:** 5030300

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

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

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

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

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

Number of indications for this application(s): 1

Indication #1: Management of moderate to moderately severe pain

Is this an orphan indication?

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

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

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._0___ Tanner Stage_____
Max_____ kg_____ mo._____ yr._<12___ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☒ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other: Drug product does not represent a meaningful therapeutic benefit for pediatric patients less than 12 years of age and it is unlikely to be used by a substantial number of patients in this age group.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._12___ Tanner Stage_____
Max_____ kg_____ mo._____ yr._16___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Sponsor proposes to conduct a pharmacokinetic (PK) assessment in this patient population to address whether the PK profile is consistent with that observed in adults. The program is to be initiated upon approval of the drug in the adult population.

Date studies are due (mm/dd/yy): to be determined

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: **NDA 21-745**
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 6-23-2005)

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

/s/

Paul Balcer
9/22/2006 07:31:58 AM

On behalf of Labopharm Inc., I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with the application NDA 21-745 for Tramadol Contramid® OAD (tramadol hydrochloride) tablets.

Sylvie Bouchard, MD, PhD
VP Clinical Development
Labopharm Inc.

2005/11/02
Date

Becky Prokipcak, PhD
Sr. Director, Regulatory Affairs
US Agent, CanReg Inc.

Oct 20, 2005
Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada Inc.
Attention: Becky Prokipcak, Sr. Director, Regulatory Affairs
450 North Lakeside Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

I refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your March 31, 2008, request for formal dispute resolution was received on March 31, 2008. The appeal concerns the totality of evidence provided to support the approval of Ryzolt for the management of moderate to moderately severe pain. In your request, you ask the Center for Drug Evaluation and Research (CDER) to '...direct the Division to resolve with the Company any outstanding labeling issues and approve the Ryzolt 505(b)(2) application.'

Your request appeals the decision taken by Dr. John Jenkins, Director, Office of New Drugs (OND) in CDER on January 18, 2008, to uphold the approvable action taken by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP, 'the Division') on May 30, 2007. Dr. Curtis Rosebraugh, Director, Office of Drug Evaluation II, had previously upheld the approvable action is his letter dated November 20, 2007.

I have carefully reviewed the materials you have submitted in support of your appeal as well as the internal FDA documents related to your previous submissions (e.g., medical and statistical reviews, approvable letters), including the additional information submitted on April 11, 2008. I have also had extensive discussions with CDER staff regarding this application, including staff from DAARP, OND, the Office of Biostatistics, and the Office of Medical Policy. Finally, I have greatly appreciated and benefited from my conversations with the staff and consultants from Labopharm, the follow-up email communications, and the additional materials submitted after our meeting on May 12, 2008.

I have now completed my review of the formal dispute resolution request and conclude that the scientific and regulatory standards applied by OND were appropriate. I therefore concur with Dr. Jenkins' decision dated January 18, 2008, conclude that the available data are not adequate to support approval of Ryzolt, and deny your appeal.

To summarize my conclusions and recommendations (these points then will be discussed in the paragraphs following):

i. I agree with Drs. Rosebraugh and Jenkins that communications about the expectations of the Division could have been better. However, the Division has clearly communicated the issues they had with analyses that 'give credit' to patients who discontinued early from the trial, including Last Observation Carried Forward (LOCF).

ii. Additional analyses conducted to date, including analyses using Time Weighted Average and Completer Analysis, have not sufficiently addressed this concern.
iii. In the absence of sufficient support for the robustness of the LOCF analysis in the pivotal study (MDT3-005), the other data do not provide a 'weight of evidence' sufficient to support the approval of Ryzolt.
iv. The Ryzolt application has not been held to a higher standard than that applied to other, similar products.
v. While there may be other analytical approaches that could be successful, I strongly recommend the prompt submission of the statistical analysis suggested by Dr. Jenkins in the form of a Complete Response[1]. A positive finding on this analysis will provide the needed assurance to support the efficacy of Ryzolt for the proposed indication. Following resolution of any issues that were not discussed in this appeal (e.g., labeling, manufacturing), such a finding will lead to the approval of Ryzolt.

DISCUSSION

In discussing these points, I'm first going to follow the flow of the email sent by Dr. Howard-Tripp to me on May 29, 2008, as I believe it neatly outlines the thrust of the arguments made by the company in support of their position. To summarize the points in Dr. Howard-Tripp's email:

1. A Special Protocol Assessment was agreed to by the FDA, and needs to carry weight in later decision-making.
2. The need for sensitivity analyses to buttress the LOCF analysis is agreed to broadly. The issues are what sensitivity analyses should be performed and, once agreed to, what they show. In this regard, your email points to two potential analyses that you believe are free from the issues raised by the Division about the LOCF method: Time-Weighted Average analyses and the Completer Analysis.
3. You also raise the analysis proposed by Dr. Jenkins. While recognizing that I cannot comment on the results of that analysis as they have not been reviewed by the FDA, you cite it as another analysis that is free from the issued raised by the Division about the LOCF method.

Before proposing a way forward, I will also discuss two other issues you've raised in your various communications:

1. 'Weight of evidence' arguments in support of the approval of Ryzolt.
2. Regulatory review standards and whether there is a level playing field being applied to this application.

Special Protocol Assessment

As you have discussed in your submissions, and as has been commented on by Drs. Rosebraugh and Jenkins, the development of Ryzolt has taken place during a time of change both in terms of the FDA organization and in terms of our thinking about the development of products for the treatment of pain. It has also taken place during a period when we have recognized the challenges of missing data. Recognizing this, you quite correctly sought certainty regarding the design and the statistical analysis of the pivotal study by submitting a Special Protocol Assessment. As we discussed when we met, I strongly support the use of SPAs for precisely this reason. Having reviewed the record in detail, and

[1] In the letter from Dr. Jenkins dated January 18, 2008, page 5.

notwithstanding the statement by the FDA that the SPA was acceptable[2], important ambiguities remained that have been the source of considerable discussion, in particular ambiguities about precisely what would constitute appropriate sensitivity analyses. There were, however, additional conversations about sensitivity analyses that communicated that this issue was not resolved by the SPA, although here again it appears that clearer discussion of methods and expectations could have been useful[3]. The Division did clearly communicate that the sensitivity analyses were needed to evaluate the impact of the imputation of 'positive' values for study dropouts that occurs in an LOCF analysis. While FDA takes the agreements it makes under SPA very seriously, I conclude that it is these ambiguities, not a failure on the part of FDA to honor its commitments or lack of effort by any party, that are the source of much of the discussions since the original action.

Additional Sensitivity Analyses

In your recent submissions, you've focused on two additional analyses as providing the needed evidence for the 'sensitivity' of LOCF in study MDT3-005[4]: the Time-Weighted Average (TWA) analyses and a Completer Analysis. I won't comment on the other three 'sensitivity analyses' you submitted, as they have been discussed by Dr. Rosebraugh and I agree with his criticism of their use. I also won't discuss Dr. Jenkins' suggested analysis here, but will return to it later. For the reasons discussed below, I conclude that neither the TWA nor the Completer Analysis are appropriate sensitivity analyses to provide evidence supporting the LOCF finding from MDT3-005.

Time-Weighted Average (TWA)

As you have pointed out, our statisticians have agreed that an analysis using TWA, especially the analysis using Baseline Observation Carried Forward (BOCF), does provide statistical evidence that patient treated with tramadol had less pain than patients who were in the placebo group over the period of the trial MDT3-005[5]. The difficulty with the use of this finding is, as you have suggested, not statistical but rather related to the appropriateness of this analysis to support the clinical interpretation of the 12-week study data as a 'surrogate' for chronic use. In this case, like the LOCF analysis, the FDA has concluded that TWA, whether using the LOCF or the BOCF method, can be driven by differences between groups in intermediate outcomes, including patients who later dropped out[6]. As the Division has discussed with you, they have concluded that such differences should not drive the analysis. Instead, the Division has focused attention on the group differences at the end of the study, as a surrogate for the chronic use of the product. As a result, TWA does not provide the needed additional support for the robustness of the primary (LOCF) analysis or the long-term efficacy of tramadol in the study required by the Division for this clinical area. In contrast, the method proposed by Dr. Jenkins imputes endpoint scores to patients in either group who did not complete the trial, using data from patients in the placebo group who did complete the trial. Intermediate scores for patients in either treatment group who dropped out prior to the end of the trial are not included. Unlike a completer analysis, this analysis compares all patients randomized between treatment groups. In addition, it does not attribute inappropriately favorable outcomes to patients who dropped out before the end of the trial. It would therefore serve as an adequate sensitivity analysis for the LOCF primary analysis in this clinical setting.

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[2] In letter dated December 6, 2004.
[3] Referenced in your letter dated April 11, 2008, page 13 and in Dr. Jenkins' letter dated January 18, 2008.
[4] Like Dr. Jenkins, I find the need for these analyses reinforced by the relatively small absolute numerical difference between the drug and placebo for the primary endpoint of study MDT3-005 (-0.479 units using LOCF).
[5] In an email from Frank Sasinowski dated May 29, 2008.
[6] In your email dated May 29, 2008 you cite Dr. Janet Wittes, who concludes that TWA-BOCF does not impute positive values to subjects when they are not on drug. This is true, but I'm making a different point, related to the contribution of patients to a TWA analysis who later withdraw from the trial.

Completer Analysis

You've also discussed using a Completer Analysis as an additional sensitivity analysis to support the use of the LOCF primary analysis in study MDT3-005. Here, as before, the issues with this type of analysis are how to interpret the data one gets from this analysis and the extent to which the analysis addresses the fundamental need to understand the efficacy of Ryzolt to the end of 12 weeks of therapy. The people in the placebo group who complete a pain trial differ from the patients who complete the trial receiving active drug in anticipated and unanticipated ways. For instance, in MDT3-005, there was a considerable drop-out rate (averaging around 25% in both groups) and there are relevant differences for patients dropping out of the trial prematurely (e.g., twice as many drop-outs for adverse events in the Ryzolt group), both factors that undermine the use of Complete Analysis as an efficacy analyses to support the robustness of the LOCF methodology. I've also talked with the Division, and with you, seeking to identify any reasons why a Completer Analysis should be afforded more weight in this therapeutic area than would be applied in other areas, but I have not been able to find a reason to do so. As a result, I conclude that a Completer Analysis cannot provide additional support for the robustness of the primary (LOCF) analysis or the long-term efficacy of tramadol in the study required for this clinical area.

Weight of Evidence Standard

Your submissions have also made arguments based on the totality of the data collected for Ryzolt (e.g., pharmacokinetic data, data from other clinical trials), arguing that this totality also supports the approval. Here, I have to agree with Dr. Jenkins: we need to start with the adequate demonstration of efficacy, and that standard has not been met in MDT3-005, which you clearly intended to serve as the pivotal demonstration of efficacy. As a result, I conclude that we cannot look to these other sources of data without first concluding that the efficacy of Ryzolt is demonstrated in study MDT3-005.

Regulatory Review Standards

I take your concerns related to 'level playing field' very seriously, and have carefully reviewed the record and discussed with the Division to compare the approach taken in this application with that taken in other relevant situations in development of pain medications[7]. In short, I find no evidence that your product was held to a different standard than was applied to other products. How to adjust for missing data is an issue that the Agency is grappling with, but I do not believe those discussions have adversely affected your product. I conclude that the suggestion made by Dr. Jenkins, while it does not originate with him, is very innovative and represents a creative and acceptable advance in this difficult field.

Regulatory Path Forward

In the end, the FDA needs to conclude that the findings based on the LOCF method from study MDT3-005 are in fact a reflection of the drug's effectiveness and that the finding will adequately inform the chronic use of Ryzolt. The analytical approaches you have proposed to date, as well as the additional analyses conducted by the FDA to assign missing values for patients who dropped out[8], have not been adequate to support that conclusion. While there are potentially other analytical approaches that could provide that reassurance, Dr. Jenkins has proposed an approach that I strongly recommend you conduct

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[7] This includes the development program for Ultram ER which Dr. Rosebraugh discussed as well as the innovator approval, which you cited in your submission dated April 11, 2008.

[8] In the email from Frank Sasinowski dated May 29, 2008, you express some frustration that internal FDA reviews could not be shared with the company. I would be happy to discuss this issue further with you if that would be useful to you.

promptly and submit the results to the Agency in the form of a Complete Response.[9] I conclude that a positive finding using this analysis will provide the needed assurance to support the efficacy of Ryzolt in the proposed population. Following resolution of any issues that were not discussed in this appeal (e.g., labeling, manufacturing), such a finding would lead to the approval of Ryzolt. I know that the Division will work to complete its review of the Complete Response in a timely manner so this issue can be brought to a fair resolution.

I am grateful for the extensive conversation we had and believe I have been scrupulous in addressing your concerns. I would be happy to discuss any aspects of this letter if you would find that useful. If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Andrew C. von Eschenbach, Commissioner, Food and Drug Administration. The appeal should be sent through the Office of the Ombudsman, FDA, at 301-827-3390.

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Deputy Director
Center for Drug Evaluation and Research

[9] The proposal is based on his discussions between Dr. Jenkins and the Office Biostatistics within the Office of Translational Sciences, and is outlined in his letter dated January 18, 2008.

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

/s/

Doug Throckmorton
6/27/2008 11:21:05 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21745 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Ryzolt Established/Proper Name: tramadol hydrochloride extended-release tablets Dosage Form: 100, 200, 300 mg		Applicant: Labopharm Agent for Applicant (if applicable): CanReg
RPM: Kathleen Davies		Division: HFD-170

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 20-281 Provide a brief explanation of how this product is different from the listed drug. It contains both an immediate-release and extended-release component. The RLD is immediate-release only. ☐ If no listed drug, check here and explain: **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.** ☒ No changes ☐ Updated Date of check: 12/10/08 **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	January 2, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE, 9/28/06, AE 5/30/07
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

[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.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP • If yes, exception for review granted *(file Center Director's memo in* Administrative/Regulatory Documents *section, with* Administrative Reviews*)* • If yes, OC clearance for approval *(file communication in* Administrative/Regulatory Documents *section with* Administrative Reviews*)*	☐ Yes ☒ No ☐ Yes ☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: ☐	
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (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.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs 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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☒ No paragraph III certification Date patent will expire
• [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)).*	☒ N/A (no paragraph IV certification) ☐ 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).

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
Copy of this Action Package Checklist[3]	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/nonconsent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AE, 9/28/06, AE 5/30/07
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	X
❖ Original applicant-proposed labeling	X
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	X
❖ Most recent applicant-proposed labeling	X
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEDP 6/9/06, 7/14/06, 9/1/06, 9/22/06, 4/13/07, 9/25/08 ☐ DRISK ☒ DDMAC ☒ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	9/11/06
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	☒ Not on AIP
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	

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

Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10/30/08
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	9/23/06
• Clinical review(s) *(indicate date for each review)*	5/16/07, 9/21/06
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another 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	clinical
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not needed 8/29/06
❖ REMS • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • Review(s) and recommendations (including those by OSE and CSS) *(indicate location/date if incorporated into another review)*	☒ None .
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	9/18/06, 9/20/06,9/21/06
• Bioequivalence Studies	N/A
• Clinical Pharmacology Studies	N/A
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 9/15/08, 4/24/07, 8/1/06
Clinical Pharmacology ☐ None	
• Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/10/08, 5/11/07, 8/24/06
❖ DSI Clinical Pharmacology Inspection Review Summary	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 12/5/08
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 8/3/06
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/TeamLeader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 5/11/07, 9/20/06, 1/20/06
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☒ Acceptable ☐ Withhold recommendation
• BLAs: ➢ TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within*	Date completed: ☐ Requested

60 days prior to AP)	☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada Inc.
Attention: Becky Prokipcak
Sr. Director, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablet.

We refer also to your March 31, 2008, request for formal dispute resolution received on March 31, 2008. The appeal concerns the totality of the evidence provided to support the approval of Ryzolt for the management of moderate to moderately severe pain. In addition, we refer to the information submitted and received April 11, 2008, that was requested during our April 8, 2008, conference call with Mr. Frank Sasinowski and Ms. Anne Marie Murphy, counsel for Labopharm Inc.

In your appeal you request a meeting to discuss this matter. We are granting your request, and as per communication with Ms. Murphy, we have scheduled the following meeting with you to discuss the issues.

Date: Monday, May 12, 2008
Time: 11:00 AM -12:30 PM EDT
Location: White Oak Building #22, Room 1313
10903 New Hampshire Avenue
Silver Spring, MD

CDER participants (invited): Drs. Douglas Throckmorton, John Jenkins, Curtis Rosebraugh, Bob Rappaport, Sharon Hertz, Robert Temple, Robert O'Neill, Thomas Permutt, Dionne Price, Yongman Kim, and Ms. Kim Colangelo and Kathleen Davies.

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please email a list of attendees to Michele Brown at Michele.Brown@fda.hhs.gov, so that we can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards the following number to request an escort to the conference room: OND Immediate Office, 6-0700.

If you have any questions, please call me at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

Kim M. Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
Formal Dispute Resolution Project Manager
Center for Drug Evaluation and Research

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

/s/

Kim Colangelo
4/24/2008 03:19:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada Inc.
Attention: Becky Prokipcak
Sr. Director, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

I refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your December 19, 2007, request for formal dispute resolution, received on December 19, 2007, concerned the approvable action taken by the Division of Anesthesia, Analgesia, and Rheumatology Products on May 30, 2007, and the decision by Dr. Curtis Rosebraugh, Director, Office of Drug Evaluation II, to uphold this decision on November 20, 2007.

In your request for dispute resolution you state that:

1. The data submitted well exceed the standard for approval of a 505(b)(2) application of a new formulation of a listed drug;
2. Study MDT3-005 was designed, conducted, and analyzed according to a binding agreement under a special protocol agreement (SPA);
3. You refute the Division's contention that only individuals who cannot tolerate Ryzolt derive benefit from it;
4. You question whether there is a level playing field; and
5. You ask that I overturn the decision of the Division and ODE II that efficacy has not been demonstrated and direct the Division to resolve with the company any remaining labeling issues.

I have carefully reviewed the information provided in support of your conclusions and requested action. I have been briefed on the application and the issues in dispute by staff from the Division of Anesthesia, Analgesia, and Rheumatology Products[1] (DAARP, the Division), the Office of Drug Evaluation II, and the Office of Biostatistics. I have also consulted with Dr. Robert Temple, Director of the Office of Medical Policy, and Dr. Robert O'Neill, Director of the Office of Biostatistics to obtain their counsel on this complex case.

[1] Your initial interactions were with staff in the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, which was merged with the Division of Anesthetic, Critical Care, and Addiction Drug Products to form the current Division of Anesthesia, Analgesia, and Rheumatology Products in 2005.

After careful review and consideration I conclude that you have not met the statutory standard for demonstration of efficacy for your sustained-release tramadol drug product. Therefore, you appeal is denied. I have, however, identified what I believe is an appropriate path forward for further review of this application that may obviate the need for additional clinical trials. I will briefly summarize the basis for my conclusion and my proposal for the path forward.

First, as you correctly note, an application submitted under 505(b)(2) "need contain only that information needed to support the modification(s) of the listed drug."[2] The ability to reference the Agency's previous findings of safety and efficacy for a listed drug, however, does not alter the requirement that the sponsor of the modified drug product meet the statutory standard of "substantial evidence" as defined in section 505(d) of the Food Drug and Cosmetic Act and in our Guidance[3]. In other words, 505(b)(2) applications are held to the same statutory standard for approval as 505(b)(1) applications.

At the time you sought advice from the Division on the development of a sustained-release tramadol product there were no approved sustained-release tramadol products. You proposed to reference the Agency's previous finding of safety and effectiveness for immediate-release tramadol and submit a 505(b)(2) application. The Division agreed that this was an appropriate development strategy and made clear to you that approval of a sustained-release tramadol product would require adequate and well-controlled clinical trials that demonstrated the safety and effectiveness of the new product for the proposed indication. This advice was reasonable and consistent with multiple other cases where the Agency has required controlled clinical trials to support approval of a sustained-release formulation of a previously approved drug substance. While not the sole basis for the requirement for controlled clinical trials in support of approval, the pharmacokinetic differences between your sustained-release product and the approved immediate release product supported the need for controlled clinical trials to assess both safety and efficacy. In particular, the lower plasma levels seen with your product at the beginning and the end of the 24 hour dosing interval raised significant questions regarding whether your product would be effective throughout the dosing interval.

Since your initial interactions with the Division on this issue the Division has undergone reorganization and changes in leadership as well as further evolution in its thinking on the types of clinical trials needed to support approval of drugs for a chronic pain indication. This evolution has included a rethinking of the number of trials needed to support the approval of your product such that today it is agreed that one adequate and well-controlled clinical trial that the Division concludes demonstrates efficacy would be adequate to support approval (assuming other issues such as safety or manufacturing concerns were not identified that precluded approval). Since the Special Protocol Assessment (SPA) referenced in your submission related to Study MDT3-005, and this study was intended to be the pivotal demonstration of efficacy, I will focus my attention on evaluating why I agree with the Division's assessment that this study, as currently analyzed, does not represent the required positive, controlled clinical trial.

Despite your frequent references to application of "podium policy" and "post-hoc" analyses by the Division, my reading of the record shows that the Division communicated to you on multiple occasions its concerns about the proposed plans for the analysis of the primary endpoint for Study MDT3-005. The Division clearly communicated its expectation that the primary efficacy analysis for Study MDT3-

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[2] 21 CFR 315.54
[3] Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998.

005 would be a comparison of change from baseline to study endpoint (last visit) between the extended-release tramadol and placebo groups for the selected primary efficacy variable the Pain Intensity Score Numerical Rating Scale (PI-NRS). The Division also clearly communicated its concern that the primary analysis not be biased in favor of the drug due to imputation of "positive" values at study endpoint for patients who dropped out of the study before completion. While is clear that as part of the SPA process the Division accepted your proposal to use Last Observation Carried Forward (LOCF) as your preferred imputation method for handling missing values for the primary analysis, the Division also made clear on multiple occasions that it would be necessary to conduct sensitivity analyses to evaluate the impact of the imputation of "positive" values for study drop outs on the primary analysis. Since the primary analysis for Study MDT3-005 showed a statistically significant difference compared to placebo using LOCF, the primary issue in dispute between you and the Division relates to the proper "sensitivity" analyses to be conducted to assess the impact of the imputation method on the results of the study. Since the Division made this very concern clear to you throughout the interactions regarding development of the protocol for Study MDT3-005, I do not agree with your assessment that the Division's acceptance of LOCF as the imputation strategy for the primary efficacy endpoint binds the Division to approve your application simply because the primary analysis was positive. To the contrary, the Division provided you with more than adequate warning of its intention to carefully assess this issue during its review of the study results and never provided any guarantee that a positive result on the primary endpoint when using LOCF would be interpreted as a "win."[4]

You point to several positive pre-specified secondary endpoints in support of your assertion that efficacy was demonstrated in Study MDT3-005. Until a convincingly positive primary analysis is demonstrated, I consider these analyses to be supportive. The real question in dispute revolves around whether the LOCF imputation method unfairly biased the primary analysis in favor of the drug by imputing positive values for missing data. It is my understanding that what the Division was interested in seeing as sensitivity analyses were re-analyses of the primary endpoint using different methods for imputation of missing values to assess how "sensitive" the findings were to the imputation method used. This interpretation of the meaning of sensitivity analyses is supported by the Division's selection of Baseline Observation Carried Forward (BOCF) as its recommended analysis for this study; i.e., a method where the patient's baseline value is imputed for missing endpoint data as opposed to the patient's last observed value on treatment before drop out from the study. In the Division's sensitivity analysis the focus remains on the pre-specified primary endpoint of change from baseline to study endpoint, which re-emphasizes the Division's view that efficacy needed to be demonstrated at the end of the study period to support approval for an indication for chronic pain. Using BOCF the study failed on the primary efficacy analysis.

In your resubmission of the application in response to the approvable letter you conducted additional sensitivity analyses, some of which were of the type that the Division was seeking and similar to those suggested to you by the Division in a meeting on February 24, 2004. According to the Agency's minutes of that meeting you posed the following question:

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[4] The strict interpretation you propose for what it means when the Division "agrees" with a protocol and a statistical analysis plan (SAP) under an SPA would also require that the Division adhere to your definition of the "minimum between-group difference considered clinically significant in Pain intensity score as measured by the 11-point PI-NRS rating = 1" as defined in your protocol and you SAP. I would note that your preferred primary analysis of Study MDT3-005 using LOCF resulted in an absolute numerical difference between the drug and placebo group of -0.479, far below the minimum clinically significant difference of 1 you defined.

> "Does the Agency concur with the LOCF as the imputation method for handling missing data as the result of dropouts?"

The Agency's response was:

> "No, we don't agree that last observation carried forward (LOCF) should be the only method of imputation. The reasons for dropouts should be reported, and sensitivity analyses using alternative imputation methods should be performed. One example: cross group imputation analyses where a missing value in the treated group is imputed by the mean value or a random value of the placebo group and a missing value in the placebo group is imputed by the mean value or a random value of the treated group. More than one imputation method should be used for imputing missing values."

You did submit sensitivity analyses based on "placebo mean (estimate of trajectory)" and "placebo median (estimate of trajectory)" and reported these analyses as statistically significant at the $p<0.05$ level. I find use of the placebo group data for imputation of missing values to be an appropriate method for a sensitivity analysis since there was a very large placebo response in Study MDT3-005 and using some measure of the placebo response is less conservative than imputation of baseline values, which could be viewed as representing a "worst case" sensitivity analysis. I find this particularly true in this specific case since the design of Study MDT3-005 required, apparently at the Division's urging, fixed dosing throughout the study period and did not allow titration of the dose for either lack of efficacy or adverse events. In such a study design the only option for patients who experience intolerable side effects from the drug was to discontinue from the study and I agree that BOCF may be an overly conservative imputation method in such a case. I would emphasize that this conclusion is limited to this particular study, and that I do not think that use of BOCF is inappropriate in a study that allows for dose titration as a way to minimize drop outs due to lack of efficacy or adverse effects.

The Division considered your new sensitivity analyses based on imputation of placebo group data, however, they concluded that the methodology that you used to conduct the analysis was flawed. In your analyses you assumed that a patient on active treatment who had already improved, perhaps by a significant amount from baseline, would then continue to improve when treatment was discontinued at the same rate that placebo patients improved from baseline. Applying such a methodology biases the analysis in favor of showing an effect of the active drug, and in some cases actually resulted in your imputation of endpoint values of pain scores less than zero (although you "corrected' this by simply imputing zero pain). I concur with the Division's conclusion that these analyses using placebo group data for imputation of missing are fundamentally flawed and uninterpretable.

The Division concluded that while the pre-specified primary analysis is positive when LOCF is used to impute missing values you have not satisfactorily addressed its concerns that this positive result may be due to imputation of good scores to patients who dropped out of the study early because they were not able to tolerate the drug. The Division further concluded that you have not demonstrated efficacy at the end of the study period, a requirement that has been consistently applied to other drugs seeking an indication for chronic pain during the time period that your drug has been under development and review by the Division. I concur with these assessments and I believe that the Division has fairly applied these criteria for other recent development programs and application reviews for drugs seeking an indication for chronic pain (i.e., there has been a level playing field).

As I noted earlier, I believe that there is a role for the use of data from the placebo group for imputation of missing values and I believe that such an analysis, if properly conducted, would be a fair approach to the sensitivity analysis the Division has required for Study MDT3-005. I have consulted with staff from the Office of Biostatistics regarding a possible way to conduct such an analysis and the proposed method is described in some detail below. As a path forward I recommend that you reanalyze the primary endpoint for Study MDT3-005 using the method of imputation described below and resubmit this analysis as a complete response to the most recent Approvable Letter (along with any other data and updates necessary for such a resubmission to be considered a complete response). If such an analysis is positive it could help reassure the Division that the outcome of the study is not biased by the imputation of good scores for patients who drop out before completing the study and provide the sensitivity analysis requested in support of approval. I strongly advise that you request a meeting with the Division in advance of your resubmission to ensure that you fully understand their proposed method for use of placebo group data for imputation of missing values and reach agreement on any other analyses to be included in the resubmitted application. In addition to the new primary analysis, I would recommend that you submit a continuous responder analysis using the placebo imputation method described below.

The recommended imputation method using placebo group data is as follows:

Missing data at end of study will be imputed by scores drawn randomly from the placebo observations at end of study rather than by baseline scores. Specifically:

1. Stratify the placebo completers in tertiles with respect to outcome: upper third, middle third, lower third.
2. Stratify the combined active and placebo groups by tertile with respect to baseline score.
3. For each missing observation at week 12, substitute a random score from the placebo completers, drawn from the same tertile that the baseline score for that individual fell into.
4. Conduct the protocol-specified primary analysis on the now complete data set.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Janet Woodcock, Acting Director, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo. Any questions concerning your appeal should be addressed via Ms. Colangelo at (301) 796-0140. Questions regarding next steps with the Division as recommended in this response should be directed to Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D., F.C.C.P.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

John Jenkins
1/18/2008 02:29:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada Inc.
Attention: Becky Prokipcak
Sr. Director, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Prokipcak:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablet.

We acknowledge receipt on December 19, 2007, of your December 19, 2007, request for formal dispute resolution concerning the approvable action taken by the Division of Anesthesia, Analgesia, and Rheumatology Products on May 30, 2007, and the decision by Dr. Curtis Rosebraugh to uphold this decision on November 20, 2007.

Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this FDRR is due on or before January 18, 2008.

This FDRR has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301)796-0140.

Sincerely,

{See appended electronic signature page}

Kim M. Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Beth Duvall-Miller
12/21/2007 12:36:54 PM
On behalf of Kim Colangelo

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, PhD, RAC
Senior Director, Regulatory Affairs

Dear Dr: Prokipcak:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt™ (tramadol hydrochloride) extended-release 100, 200 and 300 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 8, 2007. The purpose of the meeting was to discuss the issues set forth in your formal dispute resolution request (FDRR), received October 15, 2007, with Dr. Rosebraugh, Acting Director of Office of Drug Evaluation II.

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) 796-2205.

Sincerely,

{See appended electronic signature page}

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

Enclosure

SPONSOR MEETING MINUTES

MEETING DATE: November 8, 2007

TIME: 2:00 – 3:00 PM (EST)

LOCATION: Food and Drug Administration, Bldg. 22, Room 1309
10903 New Hampshire Ave, Silver Spring, MD 20993

APPLICATION: NDA 21-745

PRODUCT: Ryzolt (tramadol hydrochloride) extended-release 100 mg, 200 mg, 300 mg tablets

INDICATION: Treatment of moderate to moderately severe pain

SPONSOR: Labopharm Canada Inc. (c/o CanReg, Inc.)

TYPE OF MEETING: Type A

MEETING CHAIR: Curtis Rosebraugh, MD MPH, Acting Director, Office of Drug Evaluation II

MEETING RECORDER: Kathleen Davies, MS, Regulatory Health Project Manager

FDA Attendees	Title
Curtis Rosebraugh, MD MPH	Acting Director, Office of Drug Evaluation II
Bob Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, MD	Deputy Division Director, Division of Anesthesia, Analgesia and Rheumatology Products
Robert O'Neill, PhD	Director, Office of Biostatistics
Thomas Permutt, PhD	Director, Division of Biometrics II
Dionne Price, PhD	Statistical Team Leader, Division of Biometrics II
Janice Weiner, JD MPH	Office of Regulatory Policy
Elizabeth Dickinson, JD	Office of Chief Counsel
Leah Ripper	Associate Director for Regulatory Affairs, Office of Drug Evaluation II
Kathleen Davies, MS	Regulatory Health Project Manager
Sharon Turner-Rinehardt	Regulatory Health Project Manager
Jane Gilbert, MD	Medical Reviewer
Labopharm Attendees	**Title**
James Howard-Tripp	President and C.E.O.
Lynda Covello	General Counsel and Corporate Secretary
Sylvie Bouchard, MD PhD	Vice President, Clinical Development and Regulatory Affairs
Robert A. Dormer, Esq	Hyman, Phelps & McNamara, P.C.

Elias Nyberg, DVM, MBA	Global Head of Regulatory Affairs
Anne Tomalin, BA, BSc	Consultant to Labopharm, CanReg Inc.
Frank Sasinowski, Esq	Hyman, Phelps & McNamara, P.C.
Anne Marie Murphy, Esq	Hyman, Phelps & McNamara, P.C.
Sybil Robertson	Deputy Head, Medical Affairs

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BACKGROUND:
Labopharm Canada Inc. requested a type A meeting to discuss the FDRR received October 15, 2007. Specifically, Labopharm requested the meeting to present to Dr. Rosebraugh their issues concerning the approvable actions issued by the Division of Anesthesia, Analgesia and Rheumatology Products in September 2006 and May 2007.

The Sponsor outlined key points of discussion in their FDRR, which they presented to Dr. Rosebraugh at the meeting. Each of the Sponsor's issues is presented below in italics, followed by a record of the general discussion at the meeting in normal font. The Office of Drug Evaluation II provided a written response to the FDRR on November 20, 2007.

Issue 1. *The statutory standard for approval has been met.*

Issue 2. *The Division failed to comply with agreed upon terms under a Special Protocol Assessment (SPA).*

Issue 3. *The statistical methods used by the company are sound, and the post hoc analyses conducted by the Division should not apply here.*

Issue 4. *Labopharm's formal and informal efforts to resolve this matter with the Division have failed.*

General Discussion:
The Sponsor began the discussion explaining their rationale as to why their application should be approved, by stating that the Special Protocol Assessment (SPA) was negotiated with the Division in order to freeze things in time for their development program. The Sponsor elaborated by explaining the history of their development program and the changing advice given by the Divisions. The Sponsor felt that incorporation of a SPA would be a "lock" with regards to the changing standards of the Agency. The Sponsor further explained that they believed a SPA agreement was reached, including an agreed upon Statistical Analysis Plan (SAP) for their pivotal Phase 3 study MDT3-005, and thus initiated the study.

The Sponsor analyzed the data using various statistical methods, with last observation carried forward (LOCF) as the primary imputation strategy, supported by various sensitivity analyses. Of the varied sensitivity analyses, the Sponsor states that four of the six methods employed showed significance and believe this supports the primary analysis with LOCF for approval. The Sponsor concluded by stating that, although pharmacokinetics could have sufficed for a 505(b)(2) application for tramadol, they instead conducted two clinical trials and have a SPA agreement. Because of this weight of evidence, the Sponsor stated that an approval should be

granted based on the SPA agreement of 2004 and to uphold the SPA precedent in the absence of any public health concerns for the tramadol products.

Dr. Rosebraugh noted the SAP was not included in the briefing package for him to review and comment on; he requested a copy be sent to him. He followed up by asking the Division to respond to the Sponsor's comments.

Dr. Hertz stated that she was present for SPA negotiations in 2004. The Division reiterated that the concern about imputation of missing data was conveyed to the Sponsor at that time, but possibly not well documented. The major concern stated by the Division was imputation of a good score for a bad outcome in the study. The baseline observation carried forward (BOCF) imputation strategy accounted for this possibility. All sensitivity analyses employed by the Sponsor suffer the same analysis flaw of imputing a good score for a bad outcome. The Sponsor stated that they did not believe BOCF was required from the SPA or SAP and is thus not applicable. In addition, the Sponsor stated that the BOCF technique does not take into account regression to the mean. The Division stated that BOCF was never required, but an analysis had to be performed that did not impute a good score for a bad outcome. All the proposed analyses by the Sponsor incorporated a good score for a bad outcome. The Sponsor stated that the only elements agreed upon with the Division in the SPA were the primary analysis (LOCF), time-weighted analysis and a continuous responder analysis. The Sponsor performed these analyses and believes their study shows significance and should be approved.

Dr. Rosebraugh asked Dr. O'Neill to comment on the discussion of imputation of missing data. Dr. O'Neill stated that this area of analysis is quite difficult for statisticians. The determination of whether to give partial credit or no credit for a dropout from a study is a difficult challenge. Determining what is important and interpretable, however, is not driven by statistics; it is instead driven by the clinical endpoint of interest. The statistical analysis chosen must align with the clinical outcome of interest. Furthermore, in pain trials one may consider missing data to not actually be "missing;" as the data that is not captured is informative and provides insight into the study and the drug. The Division strongly agreed with Dr. O'Neill's comments and followed up by stating that the patients that take Ryzolt must be able to tolerate the product or they will stop taking the product. From that standpoint, there is no statistical issue. It is problematic to impute a good score for a drop-out. Imputation strategies such as BOCF or a combination of LOCF/BOCF account for that issue. The Division's bottom line statement was that patients must be able to tolerate the drug for the drug to be useful.

The Sponsor argued that they were not allowed to adjust the dose during the trial and this might explain the number of dropouts. The Division stated that patients in the trial were titrated to the randomized dose depending on tolerability; therefore, there was an ability to adjust the dose. The Sponsor reiterated that they believe if they could have conducted a more flexible-dose trial, as conducted in Europe, their data would have been much more favorable with respect to dropouts.

At this point in the discussions, Dr. Rosebraugh asked the Sponsor to compare and contrast their product to the currently approved tramadol ER product. The Sponsor stated that the approved tramadol ER product was permitted to conduct a flexible-dose study design, which they believe is the reason that product was approved. The Sponsor stated their product's clinical performance

is similar to the approved tramadol ER product, and that they have a SPA with defined sensitivity analyses that show significant results. The Sponsor further expressed their discontent with the continually changing standards within the Division.

Dr. Rosebraugh concluded the meeting and stated that he would review the SAP, once submitted to him by the Sponsor, evaluate all relevant information, and make a decision regarding the FDRR within thirty days of this meeting.

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/s/

Kathleen Davies
12/11/2007 03:27:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D., RAC
Sr. Director, Regulatory Affairs

Dear Dr. Prokipcak:

Reference is made to the New Drug Application (NDA) you submitted, on behalf of Labopharm Canada, Inc., pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Ryzolt (tramadol hydrochloride) extended-release 100-, 200-, and 300-mg tablets.

Your October 15, 2007, request for formal dispute resolution (FDRR), received on October 15, concerned the approvable action taken by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) on this application, including the statistical methods used by the Agency in reaching its decision. You requested that the agency rule that the data already submitted demonstrate substantial evidence of effectiveness for approval of NDA 21-745. You also requested that a meeting be convened with me to discuss the issues set forth in your FDRR document. This meeting was granted and occurred on November 8, 2007.

In reaching my decision on your FDRR, I considered your FDRR package and the subsequent submission that I requested as well as the discussion at our November 8 meeting, information gathered from communications with DAARP staff and other personnel within the Center for Drug Evaluation and Research (CDER), and correspondence from the agency to you.

My conclusion is that I support the Division's finding that your application is approvable and that you have failed to demonstrate the efficacy of Ryzolt by providing substantial evidence for your proposed indication of the management of moderate to moderately severe pain. I will expand upon my determination below.

You list several issues in your FDRR letter that you feel support your request for approval of your application. The pertinent points include:

1. The statutory standard for approval has been met.

2. The Division failed to comply with agreed-upon terms under a Special Protocol Assessment.
3. The statistical methods used by the company are sound, and the post hoc analyses conducted by the Division should not apply here.

I will address these points in turn, although not in the order presented in your letter.

The Division failed to comply with the agreed-upon terms under a Special Protocol Assessment (SPA)

The main point of contention between the Division and you is the appropriate type of imputation strategy for the efficacy data included in your application. The focal point of the contention is how to handle drop-outs during the statistical analysis. The Division contends that someone who drops-out due to intolerance of Ryzolt should not be attributed a 'good' score as the only method of determining efficacy, because this population may be driving the results of the study. This attribution would lead to labeling that would paradoxically reflect that the drug was effective for a population that could not tolerate it. The Division feels that this outcome would present an insurmountable labeling problem.

Your contention is that you performed your analysis as part of an agreement reached under the SPA process, and that any agreement reached by this process can only be changed with written consent of the applicant or pursuant to a decision of the Director of the reviewing division that "a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun." Inherent in your statement is your feeling that, during its review, the Division changed the analysis plan that was originally agreed upon under the SPA. I do note that these agreements, and subsequent discussions and review of the application, were reached prior to, during, and after CDER undertook a reorganization, which merged the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products with the Division of Anesthetic, Critical Care, and Addiction Drug Products to form the current Division of Anesthesia, Analgesia and Rheumatology Products. I make a point of this because there have been leadership changes during the development program of your product, so it is important to determine if prior agreements have been honored, and if not, why they were not. I am also sympathetic that you seemed to have received advice that changed over time, which led to your wanting a SPA so that advice would be formalized into an agreement.

Therefore, I felt it was essential to understand the nature of your Special Protocol Assessment for study MDT3-005. In our July 23, 2004, letter, we stated:

"The method of handling missing data should be specified. Multiple approaches for a sensitivity analysis is recommended in addition to LOCF. There is no agreement at this time on which sensitivity analyses will be utilized." This statement was preceded by another: *"The time specific assessments will be considered the primary analysis and the time weighted average will be considered a secondary analysis".*

These statements indicate that we were willing to accept Last Observation Carried Forward (LOCF) as the primary analysis for the time-specific assessments, but only if it was supported by sensitivity analyses. The requirement for sensitivity analyses for support would be consistent with how the Division evaluates these products because LOCF in and by itself may allow imputation of 'good' scores for patients who drop out due to adverse events from the drug. In further correspondence, dated December 6, 2004, we stated that:

"The proposed SAP is, in general, acceptable."

I reviewed the protocol in your submitted package to see what we agreed to as acceptable. (The protocol in the submitted FDRR package is version 3, dated June 8, 2005, and may not correspond to the protocol that was agreed upon above, but was the version you submitted.) The protocol states on page 44, in section 7.2.6.1.1, "Handling of Missing or Off-Schedule Efficacy Data":

"In efficacy analyses based on the FA population, appropriate imputation methods will be used to handle missing values resulting from early discontinuation due to adverse events or lack of efficacy.

"Last Observation Carried Forward (LOCF) method will be considered the primary imputation method. Other imputation methods will be used to allow for sensitivity analyses to be performed in order to evaluate the impact of differential drop-out rates."

This would seem to be an acknowledgment on your part that differential drop-out rates have to be explored and that sensitivity analyses have to support the use of LOCF as the primary analysis. It would follow, based on interactions you have had with the Division, that subjects dropping out for drug-induced adverse events should not have a 'good' score assigned to them in the analyses. Therefore, the next vital piece of information is to determine if specific 'sensitivity analyses' in the meaning and spirit of the discussions above, were agreed to.

At our meeting on November 8, you stated that the SAP pre-specified the sensitivity analyses for the SPA. I requested that you formally submit this documentation as well as referencing the relevant text.

I have reviewed the specific additional documentation that I requested at this meeting and I do not agree that this was an agreement in regard to what sensitivity analyses would be performed as I will discuss below.

The text on Page 13, under Section 4.4 states:

"Furthermore, the Time-Weighted Average method will be used as another way to handle missing values. It will assess the average effect of treatment during the 12-week treatment. A sensitivity analysis will be performed in order to compare the results under the different methods and to evaluate the impact of potentially differential drop-out rates."

The term "sensitivity analysis" above is used to refer to an exploratory analysis of a discrepancy already found between calculations. This is different from what the division, or I, would consider a sensitivity analysis, which is performing additional calculations that might or might not reveal discrepancies. As such, I do not consider the statement above a *"sensitivity analyses to be performed in order to . . . evaluate the impact of differential drop-out rates"* as was intended by the Division in the SPA.

The text on page 17, under Section 4.5, under the heading "Time to Response" states:

"The time to response, i.e. the number of days between starting the double-blind treatment and becoming a responder, will be analysed by means of life table analysis using Kaplan-Meier estimates and Kaplan-Meier curves."

This is not a sensitivity analysis either, as defined above, but is a time to response analysis, as the heading would suggest.

I therefore do not agree with your assertion that the division failed to comply with the terms of the SPA as there seems to be an agreement that sensitivity analyses evaluating the impact of differential drop-out rates must be supportive of the LOCF analysis in order to conclude that there is efficacy. I also do not believe that there were pre-specified sensitivity analyses in the SPA. This would then lead to the question of what types of sensitivity analyses are appropriate. I will address that issue below.

The statutory standard for approval has been met

As you point out, we require manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." This is further defined in section 505(d) of the Act and in our guidance[1] as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Inherent in this statement is that "substantial evidence" is based on judgment and experience.

We do have significance experience with drugs similar to yours, which are seeking similar indications, upon which to form points of reference for comparison in determining efficacy of a product. These points of reference allow us to apply uniform standards between products, for a 'level playing field,' in coming to conclusions regarding efficacy. This experience also allows us to "fairly and responsibly" make conclusions regarding whether a sponsor's claims regarding a drug's efficacy are supported by the data. In examining the results of study MDT3-003, you clearly did not demonstrate statistical significance when using BOCF as the imputation value for

[1] Guidance for Industry. *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.* May 1998

any dose tested (100 mg, 200 mg or 300 mg). I would point out that this standard was applied to another tramadol product (Ultram ER) which did demonstrate efficacy using this imputation method. When using LOCF imputation values, the 300-mg, 200-mg and 100-mg doses demonstrated p-values of 0.016, 0.050, and 0.093 respectively. The results for the strengths that demonstrated statistical significance when the LOCF imputation method was applied were driven mainly by subjects who had to withdraw from the study due to adverse events and were unable to tolerate the medication. At best, the data from study MDT3-003 can only be considered as supportive to a showing of efficacy.

I have examined the data from MDT3-005 in detail as this study is the basis for regarding whether the terms of the SPA were violated. This study allowed an enrichment paradigm for what should have been tramadol-tolerant subjects by having an initial, open-label phase during which subjects were titrated to individual doses based on optimal efficacy and tolerability and drop outs due to adverse events or lack of efficacy were not randomized or included in the statistical analysis. This enrichment should have minimized drop-outs due to intolerance to the medication to the greatest extent possible, allowing you the best opportunity to demonstrate efficacy at the conclusion of a 12-week study. The efficacy results demonstrated that the LOCF imputation strategy did demonstrate statistical significance with a p-value of 0.016. This would partially fulfill the agreement of the SPA, but would need to be supported by sensitivity analyses that 'evaluated the impact of differential drop-out rates.' Therefore, what type of imputation would be appropriate is the key question for your application. The Division has documented that you originally did BOCF imputation as a sensitivity analysis, which failed to demonstrate statistical significance. With this failure, you then performed multiple additional sensitivity analyses including:

1) Last On-Study Observation Carried Forward (LOnStCF)
2) Placebo Mean Trajectory Carried Forward
3) Placebo Median Trajectory Carried Forward
4) Completers analysis

You have concluded that these additional sensitivity analyses confirm efficacy of your product as each, with the exception of the completers analysis which did not demonstrate statistical significance, demonstrated a $p < 0.05$. However, I do not agree with your conclusion as the use of the first three sensitivity analyses imputations all share the same methodology of attributing a 'good' score to patients who were unable to tolerate Ryzolt due to intolerance and subsequently discontinued treatment. I would therefore not consider these analyses sufficiently robust to evaluate the impact of differential drop-out rates. The Division has performed its own sensitivity analyses and when not imputing a 'good' score for drop-outs due to adverse events has been unable to demonstrate statistical significance that would support a conclusion of substantial evidence of efficacy. In particular, the Division has performed a responder analysis that I found very compelling in demonstrating lack of efficacy for Ryzolt compared to placebo for those patients able to complete the 12-week study. While Ultram ER did demonstrate a significant difference in their responder analysis (graph included in product label) when imputing drop-outs as non-responders, you did not demonstrate a difference between your drug and placebo. This assures me that the division is not holding your application to a different standard than that used to approve similar products.

We must evaluate whether a drug will have the effect "it purports" under the conditions suggested in the label. As previously conveyed to you, your studies have demonstrated that the drug seems to be deriving its efficacy from patients who cannot tolerate the adverse effects associated with its use. I have examined applications similar to yours within similar historic timeframes, both that have received approval and have not received approval, and have found that the Division has applied uniform standards across this type of product and has been consistent in the resultant actions.

The statistical methods used by the company are sound, and the post hoc analyses conducted by the Division should not apply here

This issue has been discussed above. I would just add that I have not found compelling evidence that any sensitivity analyses regarding how to evaluate the effect of drop-outs due to adverse events was pre-specified in the SPA. As such, all sensitivity analyses performed in this regard to date by either you or us would be considered post hoc analyses.

As a final matter, you also assert that the Division has been inconsistent with previous precedents. As your example, you cite Avinza (morphine sulfate extended-release capsules), which was approved March 20, 2002, for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. You state that Avinza was approved pursuant to section 505(b)(2) with a single four-week study.

In the past, we did accept applications for chronic indications that included studies of duration less than 12 weeks. However, we became concerned that this policy was inconsistent with the standard in the Office of New Drugs that chronic use drug products should demonstrate efficacy over at least a 12-week period in order to establish durability of the effect. The Avinza program was developed prior to our modification of efficacy requirements and therefore is not relevant to your situation. What is relevant, however, is that since we have instituted the 12-week study duration requirement, all applications for chronic pain indications have been asked to demonstrate efficacy at the end of this time period. That includes other forms of extended-release tramadol, which have been, or may be, evaluated for similar indications. While this time requirement allows us to evaluate durability of effect, it also assures us that adverse events will not prevent patients from tolerating a medication given for a chronic condition during long-term use, which is very applicable to your application.

To summarize, I appreciate that you and the Division have worked exceedingly hard to try to reconcile your differences in approach to this application, but have been unsuccessful. I am very sympathetic that during your development program you experienced changing advice. However, I cannot substitute sympathy for evidence of efficacy. I do not believe that the Division violated the terms of the SPA. In conducting a full consideration of the data, in my opinion an overview of the analysis reveals that you have not been able to demonstrate efficacy for your product for the requested indication. I do not believe it is valid to allow imputations for efficacy for pain medications to be used chronically if the patients cannot tolerate the medication and are unable to take it chronically. I have not found your arguments persuasive and I support the Division's

approvable action. I recommend you consult with the Division as to the type and design of study(ies) needed to supply the requisite data to demonstrate efficacy.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. This appeal should be sent again through the Center's Dispute Resolution Project Manager, Ms. Grace Carmouze, at the following address:

Ms. Grace Carmouze
Dispute Resolution Project Manager
Office of New Drugs
FDA, Bldg 22, Room 6460
10903 New Hampshire Ave.
Silver Spring, MD 20993

A copy should also be submitted to the NDA at the usual 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

If you have any questions concerning your appeal, contact Ms. Carmouze at (301) 796-1654.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
11/20/2007 09:47:00 AM
FDRR response

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D., RAC
Sr. Director, Regulatory Affairs

Dear Dr. Prokipcak:

We refer to the New Drug Application (NDA) you submitted, on behalf of Labopharm Canada, Inc., pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release 100-, 200-, and 300-mg tablets.

We acknowledge receipt on October 15, 2007, of a request for formal dispute resolution (FDR) submitted by Hyman, Phelps & McNamara, P.C., on behalf of Labopharm concerning the approvable action taken by the Division of Anesthesia, Analgesia, and Rheumatology Products on this application, including the statistical methods used by the Agency and your failed attempts to resolve issues with the review division.

The FDR was forwarded for review to Dr. Curtis Rosebraugh, Acting Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research.

Pursuant to the CDER/CBER draft Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have 30 calendar days from the receipt date of the formal request to respond. Therefore, our response to this FDR would be due on or before November 14, 2007. However, the FDR included a request that a meeting be convened as soon as possible to discuss the issues set forth in this document. The request for a meeting was granted and the meeting has been scheduled for November 8. Subsequently, we will respond to the FDR within 30 days of the meeting (December 8).

We will contact you should we have any questions or require additional information.

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/s/

Leah Ripper
10/26/2007 04:25:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/oCanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, PhD RAC
Sr. Director, Regulatory Affairs

Dear Dr. Prokipcak:

Please refer to your New Drug Application (NDA) dated November 25, 2005, received November 28, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release 100, 200 and 300 mg tablets.

We also refer to your October 15, 2007, correspondence, received October 15, 2007, requesting a meeting to discuss your formal dispute resolution request (FDRR) and a meeting request to discuss the content of the FDRR.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: **November 8, 2007**
Time: **2:00 – 3:00 PM (EST)**
Location: **Food and Drug Administration**
10903 New Hampshire Ave., Bldg. 22, Room 1309
Silver Spring, MD 20993-0002

CDER participants: John Jenkins, M.D., Director, Office of New Drugs
Curtis Rosebraugh, M.D. Director, Office of Drug Evaluation II (Acting)
Bob Rappaport, M.D., Director
Sharon Hertz, M.D., Deputy Division Director
Mwango Kashoki, M.D., Clinical Team Leader
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Thomas Permutt, Ph.D., Director, Division of Biometrics II
Dionne Price, Ph.D., Statistical Team Leader
Lee W. Ripper, Associate Director for Regulatory Affairs
Kathleen Davies, M.S., Regulatory Health Project Manager

Please have all attendees bring photo identification (e.g. driver's license, passport) and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at kathleendavies@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Kathleen Davies, 301-796-2205 or Margarita Tossa, 301-796-1602.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health 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/

Kathleen Davies
10/24/2007 03:38:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, PhD, RAC
Senior Director, Regulatory Affairs

Dear Dr. Prokipcak:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt™ (tramadol hydrochloride) extended-release 100, 200 and 300 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 26, 2007. The purpose of the meeting was to discuss the approvable letter dated May 30, 2007.

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) 796-2205.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Appears This Way
On Original

SPONSOR MEETING AGENDA

MEETING DATE: June 26, 2007

TIME: 1:00 – 2:00 PM (EST)

LOCATION: Food and Drug Administration, Bldg. 22, Room 1315
10903 New Hampshire Ave, Silver Spring, MD 20993

APPLICATION: NDA 21-745

PRODUCT: Ryzolt (tramadol hydrochloride) extended-release 100 mg, 200 mg, 300 mg tablets

INDICATION: Treatment of moderate to moderately severe pain

SPONSOR: Labopharm Canada Inc. (c/o CanReg, Inc.)

TYPE OF MEETING: Type A (End of Review Meeting)

MEETING CHAIR: Sharon Hertz, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Kathleen Davies, MS, Regulatory Health Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, MD	Deputy Division Director, Division of Anesthesia, Analgesia and Rheumatology Products
Mwango Kashoki, MD MPH	Clinical Team Leader
Jin Chen, MD	Clinical Reviewer
Thomas Permutt, PhD	Director, Division of Biometrics II
Dionne Price, PhD	Statistical Team Leader (Acting)
Yongman Kim, PhD	Statistical Reviewer
Janice Weiner, JD MPH	Office of Regulatory Policy
Elizabeth Dickinson, JD	Office of Chief Counsel
Robert Temple, MD	Associate Director of Medical Policy, Office of Medical Policy
Robert O'Neill, PhD	Director, Office of Biostatistics
Keith Burkhart, MD	Clinical Reviewer
Kathleen Davies, MS	Regulatory Health Project Manager
Labopharm Attendees	**Title**
James Howard-Tripp	President and C.E.O.
Sylvie Bouchard, MD PhD	Vice President, Clinical Development and Regulatory Affairs
Robert A. Dormer, Esq	Regulatory Counsel; Hyman, Phelps & McNamara, P.C.
Elias Nyberg, DVM	Global Head of Regulatory Affairs

Anne Tomalin, BA, BSc	Consultant to Labopharm, CanReg Inc.
[redacted]	b(4)
Anthony Santopolo, MD	Vice-President, Regulatory Affairs, Purdue Pharma
Frank Sasinowski	Hyman, Phelps and McNamara

BACKGROUND:
Labopharm Canada Inc. requested a type A meeting to discuss the approvable letter dated May 30, 2007.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on June 25, 2007.

To facilitate discussion between the Division and Labopharm, Labopharm provided two handouts related to study MDT3-005. The handouts are attached to these minutes.

Question 1. *Labopharm conducted Study MDT3-005 according to the approved protocol and analyzed the results according to the approved SAP. The Agency has altered its perspective on the issue of analysis in the Approvable Letter. Furthermore, Labopharm has provided on December 18, 2006 and February 2007, additional supportive statistical analysis in their Complete Response to the September 28, 2006 Approvable Letter. Given that the FDC Act and Guidance to Industry provide that the Agency is bound by the SPA, would the Agency explain how Labopharm still does not comply with the SPA?*

FDA Response:
The Division agrees that Study MDT3-005 was conducted according to the agreement reached under the SPA. However, as we communicated to you at the November 27, 2006 End-of-Review Meeting, we do not agree that your efficacy results fulfilled the conditions of the SPA. During the SPA negotiations, the Division made it clear that the primary efficacy analysis with LOCF imputation would not be acceptable if it were not supported by an analysis with a more conservative imputation method that did not assign a good score to patients who discontinued early due to adverse events. You chose the Baseline Observation Carried Forward (BOCF) imputation method and this failed to support the LOCF results.

You also chose a responder analysis as another sensitivity analysis. Again, as we discussed at the November 27, 2006 meeting, it appears that there was a misunderstanding between the Division and Labopharm as to how the responder analysis would be performed. Nevertheless, the *post hoc* responder analysis described in the MDT3-005 study report was considered inadequate because of the method used for imputation of missing data, and because the analysis did not consider all dropouts to be non-responders. The Division conducted its own responder analysis and this showed no difference between Ryzolt and placebo.

Refer to the response to Question 2 for the Division's findings regarding the additional statistical analyses submitted as part of your Complete Response to the initial Approvable Letter.

Question 2. *Would the Agency explain the reasons why in the May 30, 2007 Approvable Letter the FDA considered Labopharm's December 18, 2006 Complete Response to the September 28, 2006 Approvable Letter to be deficient?*

FDA Response:
You conducted several sensitivity analyses using various strategies. The strategies included a last-on-study carried forward method, a completers analysis, the placebo median trajectory carried forward method, the placebo mean trajectory carried forward method, and a time-weighted average analysis. Although many approaches may be used, the Division has specific interest in strategies that do not assign a treatment benefit to patients who cannot tolerate treatment for 12 weeks.

The last-on-study carried forward, placebo mean trajectory carried forward, and the placebo median trajectory carried forward methods do not address the Division's concern regarding missing data since the methods may result in favorable outcomes for dropouts due to adverse events. Furthermore, the latter methods give more benefit to early dropouts and could assign even better scores (sometimes impossibly good) than the last observation carried forward method.

Although the time-weighted analyses may provide supplemental information regarding the effect of the treatment, these analyses average results across the duration of the trial and may ascribe treatment benefit to those patients who were unable to tolerate the treatment. Thus, the time-weighted analyses do not address the division's concerns.

Based on the collective evidence using several analysis strategies, the data from study MDT3-005 along with the data from study MDT3-003 do not provide substantial evidence of efficacy for Ryzolt for the indication of moderate to moderately severe pain.

ADDITIONAL COMMENTS:
For your additional efficacy trial, the Division encourages you to consider a study design that will minimize patient dropout, and to evaluate your product in a population whose pain is less variable over time and is appropriate for treatment with tramadol. Your statistical analysis plan should incorporate appropriate imputation strategies for missing data and address the issue of multiplicity.

General Discussion:
The Sponsor expressed the desire to come to a resolution with the Division as to how to proceed with their tramadol product. The Sponsor stated that the main point of contention is whether their sensitivity analyses supported the findings of the primary efficacy analyses. The Sponsor

requested that their product be evaluated based on the Agency's earlier standards for approval of other opioid analgesic products, and not the current standards for analgesic development.

The Sponsor referenced their two handouts to discuss ways in which missing data from their clinical trials could be dealt with. The first handout showed that the cumulative dropout over time was similar for the placebo and tramadol (Ryzolt) groups in Study 005; however, the reason for dropout may have differed between the two groups (i.e. the patients who dropped out may not have been the same). The second handout showed mean pain intensity scores for the placebo and tramadol groups. The intent of the handout was to demonstrate the regression to the mean. The Sponsor stated that the baseline observation carried forward approach does not take into account the regression to the mean. Thus, the Sponsor argued that the main issue was the choice of imputation method to account for missing data. The Sponsor further argued that sensitivity analyses such as the mean/median placebo trajectory carried forward approach accounted for the regression to the mean. For Study 005, the Sponsor asserted that the mean/median placebo trajectory carried forward approach and time-weighted average analyses demonstrated efficacy of Ryzolt.

The Division stated that we understood the challenges in identifying an appropriate method for imputing missing data to gain information regarding efficacy of an analgesic; however, the Division reiterated that the analyses performed by the Sponsor provided potentially favorable outcome results to patients dropping out due to adverse events. Dr. Robert Temple followed up this statement by emphasizing that the question is not whether tramadol is efficacious for the treatment of pain; this has previously been established. In this case, the question is whether there is a treatment benefit with this extended-release formulation of tramadol (Ryzolt) when it is taken in the intended way, namely over a chronic period. Furthermore, Dr. Temple stated that it is his and he feels the Division's position that analgesics provide symptomatic benefit, and that benefit is experienced only while a patient is taking the drug. Therefore, if a patient cannot tolerate an analgesic and discontinues it, then the drug is not effectively treating the patient's pain. The Division followed up on Dr. Temple's comments by stating that assigning favorable scores to patients who drop out due to intolerability could incorrectly result in a positive finding of efficacy for the product.

The Division stated that the review team performed multiple analyses using different imputation strategies and could not find substantial evidence of efficacy of Ryzolt. The Division further explained that they compared the efficacy findings for Ryzolt to the approved extended-release tramadol product, as based on similar imputation methods, and found that the weight of evidence for the approved product was greater than what was demonstrated for Ryzolt. The Division also noted that there is a suggestion of efficacy of Ryzolt but only when there is attribution of some benefit to patients who drop out of the study. Even when just the observed data are used, the overall treatment effect is small. Overall, the limited efficacy combined with the high dropout rate due to intolerability, the adverse event profile, and additional class safety issues (e.g. seizure, serotonin syndrome) were the major factors in the Division's decision to take an "approvable" action for Ryzolt.

The Sponsor noted that a different opioid analgesic product was approved based on a study of less than 12 weeks duration, and Ryzolt showed greater efficacy than placebo at this same time period. The Division responded that approval of the other opioid analgesic product was based on

previous standards which cannot be used to assess the efficacy of Ryzolt. The Division also noted that, in comparison to the requirements that Labopharm was initially advised it would have to meet, the current requirements are much less burdensome. For example, only one adequate and well controlled trial is necessary to support this 505(b)(2) application, and replicate evidence of efficacy for each dose is not required.

The Sponsor asked the Division how to proceed with the development of this product and stated they were open to an approach if there is one for gaining approval of this product. The Division stated that suggestions for the Sponsor were listed in the May 30, 2007 approvable letter, specifically that the Sponsor conduct another efficacy trial using a study design that minimizes patient dropout or reformulate the product. A study design that minimizes patient dropout would address the problems of how to handle missing data. A flexible dosing study was suggested as one way in which patients could tolerate the product over the entire duration of the study.

The Sponsor acknowledged these recommendations and will make a determination as to how to proceed with Ryzolt. The Sponsor also asked if they could review the statistical analyses performed by the Division during its review of this product. The Division was willing to accommodate the Sponsor's request, but needed to gather further information regarding what information was releasable to the Sponsor.

POST-MEETING NOTE:

In the course of our review of your original submission and resubmission, we considered all the analyses of Study 005 that you submitted. In addition, we conducted the following analyses of the data:

1. Your primary analysis but with baseline observation carried forward (BOCF) instead of last observation carried forward (LOCF).

2. Van der Waerden test with dropouts assigned the worst ranks; i.e., continuous responder analysis with dropouts considered nonresponders.

3. A hybrid (LOCF/BOCF) imputation strategy. Dropouts for adverse events were imputed by BOCF, but dropouts for other reasons were imputed by LOCF.

4. Imputation by the mean value in the placebo group, having calculated that mean by first imputing by LOCF for dropouts in the placebo group.

5. The van der Waerden test again, but leaving out dropouts for other reasons than lack of efficacy or adverse events, still considering dropouts for those reasons as nonresponders.

We do not consider any one of these analyses by itself to be determinative. We do not suggest that success on any one of them would lead to approval, nor failure on any one to nonapproval. Nor is it a question of the numbers of successful and unsuccessful analyses. Rather, we have tried to understand the reasons these different analyses tend toward opposite conclusions. It seems to us that all the analyses that appear to show efficacy have in common that they attribute

good outcomes to some patients who dropped out. We found no substantial evidence of patients who both tolerated the drug and benefited from it, above the number of such patients in the placebo group.

ATTACHMENTS/HANDOUTS:

Sponsor's handouts from the meeting are attached.

Cumulative Dropouts Over Time (005)

	N	End of titration	Wk 3	Wk 6	Wk 12
Placebo	**214**	**8.4%**	**14%**	**20%**	**22%**
Tramadol	**431**	**8.4%**	**17%**	**21%**	**24%**

Mean Pain Intensity Scores (Scale of 0-10 [Likert])

	Baseline	End of titration	Wk 3	Wk 6	Wk 12	LOCF
Placebo	7.2	5.3	5.0	4.5	4.3	4.8
Tramadol	7.2	4.4	4.2	4.0	4.0	4.3

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/s/

Kathleen Davies
7/26/2007 02:33:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/oCanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, PhD RAC
Sr. Director, Regulatory Affairs

Dear Dr. Prokipcak:

Please refer to your New Drug Application (NDA) dated November 25, 2005, received November 28, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release 100, 200 and 300 mg tablets.

We also refer to your September 20, 2007, correspondence, received September 21, 2007, requesting a second End-of-Review meeting to discuss your position paper regarding the approvability of Ryzolt. We have considered your request and concluded that the meeting is unnecessary. We encourage you to submit the position paper and to include any additional questions you have with that submission.

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Anne Tomalin
President, CanReg Inc. (U.S. Agent)

Dear Ms. Tomalin:

Please refer to your New Drug Application (NDA) dated November 25, 2005, received November 28, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release 100, 200 and 300 mg tablets.

We also refer to your June 1, 2007, correspondence, received June 4, 2007, requesting a meeting to discuss the approvability letter dated May 30, 2007.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: **June 26, 2007**
Time: **1:00 – 2:00 PM (EST)**
Location: **Food and Drug Administration**
Bldg. 22, Room 1315
10903 New Hampshire Ave.
Silver Spring, MD 20993

CDER participants: Bob Rappaport, MD, Division Director
Sharon Hertz, MD, Deputy Division Director
Mwango Kashoki, MD, Clinical Team Leader
Jin Chen, MD, Clinical Reviewer
Dionne Price, PhD, Statistical Team Leader (Acting)
Yongman Kim, PhD, Statistical Reviewer
Janice Weiner, JD MPH, Office of Regulatory Policy
Kathleen Davies, MS, Regulatory Health Project Manager

Please have all attendees bring photo identification (e.g. driver's license, passport) and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that

information to me at kathleendavies@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Kathleen Davies, 301-796-2205 or Margarita Tossa, 301-796-1602.

Provide the background information for this meeting (three copies to the NDA) to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia
and Rheumatology Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Provide 10 desk copies to me at the following address:

Kathleen Davies
Food and Drug Administration
10903 New Hampshire Ave.
Bldg.22, Room 3143
Silver Spring, MD 20993-0002

If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 12, 2007, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, MS
Regulatory Health 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/

Kathleen Davies
6/13/2007 09:14:41 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-745

Labopharm Canada, Inc
c/c CanReg Inc.
450 North Lakeshore Dr
Mundelein, IL 60060

Attention: Becky Prokipcak, PhD, RAC
Sr. Director, Regulatory Affairs
US Agent

Dear Dr. Prokipcak:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended-release tablets, 100 mg, 200 mg and 300 mg.

We also refer to your submission dated February 28, 2007.

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

1. The Division of Medication Errors and Technical Support (DMETS) and Division of Drug Marketing, Advertising and Communication (DDMAC) find the proprietary name, Ryzolt, acceptable.

2. Revise the presentation of the proprietary name and established name to either of the following, depending on whether or not you plan to use the proprietary name Ryzolt for other dosage forms of tramadol hydrochloride:

   Ryzolt
   (Tramadol Hydrochloride Extended-release Tablets)

   Or

   b(4

3. Relocate the tablet net quantity (e.g. 30 tablets) away from the strength area to the upper right corner, e.g. area above bar coding.

4. Include a warning statement such as "The tablets should be swallowed whole with liquid and not split, chewed, dissolved, or crushed" on the principle display panel.

5. Ensure that the unit-of-use bottles (30 and 90 tablets) comply with The Poison Prevention Packaging Act, which denotes the necessity for child-resistant closure.

If you have any questions, call Paul Balcer, Regulatory Project Manager, at (301) 796-1173.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
4/23/2007 11:11:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm, Inc.
Attention: Robert A. Dormer
Counsel for Labopharm, Inc.
Hyman, Phelps & McNamara
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Dormer:

We refer to the new drug application (NDA) submitted by Labopharm, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your request for formal dispute resolution, dated and received on March 14, 2007, concerned the decision of Dr. John Jenkins, Director, Office of New Drugs, dated February 23, 2007, to not accept your appeal because you were engaged in another proceeding on the matter, specifically, your submission of a complete response to the approvable letter, dated September 28, 2006.

I have thoroughly reviewed your argument for formal dispute resolution. Based on my review, I conclude that the formal dispute resolution process should not be initiated while the matter is also pending in the division. The guidance to industry *Formal Dispute Resolution: Appeals Above the Division Level* states that the process is designed for "disputes that cannot be resolved at the Division level." You are currently engaged in resolving this matter with the Division by virtue of your submission of a complete response. If you disagree with the outcome of the ongoing review of your submission, you can appeal that decision (e.g., scientific deficiencies and/or adherence to regulatory policy and procedures) at that time (i.e., after it has been determined that the matter cannot be resolved). If your submission is approved, there will be no need for dispute resolution. It is wasteful of Agency resources and, therefore, inappropriate to appeal a decision that continues to be under active review in the Division. Therefore, your request to reconsider your December 19, 2006, appeal is denied.

Any questions concerning your appeal should be addressed via the Center's Dispute Resolution Project Manager, Ms. Grace Carmouze at (301) 796-1654.

Sincerely,

{See appended electronic signature page}

Steven Galson, M.D., M.P.H
Director
Center for Drug Evaluation and Research

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/s/

Steven Galson
4/13/2007 03:50:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm, Inc.
Attention: Robert A. Dormer
Counsel for Labopharm, Inc.
Hyman, Phelps & McNamara
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Dormer:

We refer to the New Drug Application (NDA) submitted by Labopharm, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your request for formal dispute resolution, dated and received on March 14, 2007, concerned the February 23, 2007, decision from Dr. Robert Meyer, Director, Office of Drug Evaluation II, to uphold the Class 2 designation of your complete response submission dated December 18, 2006, with a user fee goal date of June 19, 2007.

I have reviewed the materials submitted in support of your appeal, the guidance to industry, entitled "Classifying Resubmissions in Response to Action Letters", the Manual of Policy and Procedures 6020.4, entitled "Classifying Resubmissions of Original NDAs in Response to Action Letters" as well as the rationale for the classification from the Office of Drug Evaluation II (ODE II) and the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). Based on my review, I conclude that the information submitted in your complete response does not meet the criteria outlined for a Class 1 designation and that the resubmission was appropriately considered to be a Class 2 response with a June 19, 2007, user fee goal date. Therefore, your appeal is denied.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Steven Galson, Director, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Grace Carmouze. Any questions concerning your appeal should be addressed via Ms. Carmouze at (301) 796-1654.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

John Jenkins
4/13/2007 09:10:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Labopharm, Inc.
Attention: Robert A. Dormer
Counsel for Labopharm, Inc.
Hyman, Phelps & McNamara
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Dormer:

I refer to the New Drug Application (NDA) submitted by Labopharm, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your January 24, 2007, request for formal dispute resolution concerned our January 10, 2007, response to your appeal dated December 19, 2006. In your December 19, 2006, request, you appealed the approvable action taken by the Division of Anesthesia, Analgesia and Rheumatology (DAARP) on September 28, 2006. Our January 10, 2007, response stated that we would not accept your December 19, 2006, appeal because you were engaged in another proceeding on the matter; specifically, your submission of a complete response to the September 28, 2006, approvable letter. Your January 24, 2007, request appeals our January 10, 2007, decision.

I have reviewed your argument for accepting a request for formal dispute resolution while an application is under active review, and do not agree that the formal dispute resolution process should be initiated at this time. FDA's Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level," states that the process is designed for "disputes that *cannot* [emphasis added] be resolved at the Division level." You are currently engaged in resolving this matter with the Division by virtue of your submission of a complete response. If you disagree with the outcome of the ongoing review of your submission, you can appeal that decision (e.g., scientific deficiencies and/or adherence to regulatory policy and procedures) at that time (i.e., after it has been determined that the matter cannot be resolved.) If your submission is approved, there will be no need for dispute resolution. It is wasteful of Agency resources and, therefore, inappropriate to appeal a decision which continues to be under active review in the Division. Therefore, your request to reconsider your December 19, 2006, appeal is denied.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Steven Galson, Director, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo. Any questions concerning your appeal should be addressed via Ms. Colangelo at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D., F.C.C.P.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Sandra L. Kweder
2/23/2007 05:41:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
(c/o Hyman, Phelps & McNamara)
700 Thirteen Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Attention: Robert A. Dormer
Counsel for Labopharm Canada, Inc.

Dear Mr. Dormer:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride extended release) 100, 200 and 300 mg tablets.

Your request for formal dispute resolution, dated and received on January 24, 2007, concerned the decision to classify your complete response submission, dated December 18, 2006, as a Class 2 resubmission with a user fee goal date of June 19, 2007. The decision was conveyed to you in a letter, dated January 10, 2007, signed by Ms. Parinda Jani, Chief, Project Management Staff of the Division of Anesthesia, Analgesia and Rheumatology Products.

According to FDA's Guidance for Industry, entitled "Classifying Resubmissions In Response to Action Letters" (1998 edition) and MAPP 6020.4, entitled "Classifying Resubmissions of Original NDA's in Response to Action Letters," a Class 1 resubmission may contain "a minor re-analysis of data previously submitted to the application" and "other minor clarifying information," both of which are to be "determined by the Agency as fitting the Class 1 category."

As stated in the November 27, 2006 End-of-Review Conference minutes, the Division informed Labopharm that "most likely the resubmission would be classified as Class 2, with a 6-month review clock. However, review of the application may not necessarily take 6 months." Also, in its January 30, 2007 letter to Labopharm, the Division requested additional biostatistics information regarding new sensitivity analyses with respect to the placebo-trajectory strategy. Labopharm provided the response in their February 8, 2007 submission.

Based on the contents of the resubmission, the necessity to reanalyze the complete response sensitivity analyses, and the need to review two new biostatistical analyses, the Division continues to believe that a Class 2 classification is appropriate to allow a thorough review of the information to address the deficiencies in the September 28, 2006 approvable letter. I concur with that determination.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent

again through the Center's Formal Dispute Resolution Project Manager, Kim Colangelo. Any questions concerning your appeal should be addressed via Ms. Colangelo at (301) 796-0140. If you have any questions regarding the ongoing review of this application, call Paul Z. Balcer, Project Manager, at (301) 796-1173.

Sincerely,

{See appended electronic signature page}

Robert Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Robert Meyer
2/23/2007 04:28:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm, Inc.
Attention: Robert A. Dormer
Counsel for Labopharm, Inc.
Hyman, Phelps & McNamara
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Dormer:

We refer to the New Drug Application (NDA) submitted by Labopharm, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your request for formal dispute resolution, dated and received on January 24, 2007, concerned the decision to classify your complete response submission, dated December 18, 2006, as a Class 2 resubmission with a user fee goal date of June 19, 2007.

This decision was conveyed to you in a letter, dated January 10, 2006, signed by Ms. Parinda Jani, Chief, Project Management Staff, Division of Anesthesia, Analgesia and Rheumatology Products. Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," the formal dispute resolution procedures articulated in the guidance are implemented according to the regulations. These regulations (21 CFR 10.75) state that any interested person can obtain review of a decision by raising the matter with the supervisor of the employee who made the decision.

Therefore, this appeal should first be directed to Ms. Jani's supervisor, Dr. Bob Rappaport, Director, Division of Anesthesia, Analgesia and Rheumatology Products. As this appeal is not "above the division level," we do not accept your request for formal dispute resolution at this time.

If you have any questions, please call me at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

Kim M. Colangelo
Formal Dispute Resolution Project Manager
Associate Director for Regulatory Affairs
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Kim Colangelo
2/14/2007 04:06:07 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

INFORMATION REQUEST LETTER

Labopharm Canada
450 North Lakeshore Drive
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D.
U.S. Regulatory Affairs

Dear Dr. Prokipcak:

Please refer to your December 19, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride extended release tablets) 100, 200 and 300 mg.

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

As discussed at November 27, 2006 meeting, we ask that you provide the following sensitivity analyses with respect to the placebo-trajectory imputation strategy:

1. For the median placebo observation, use the median of all patients rather than of those with valid measures, counting those without valid data as bad scores. For example, if there are 99 patients in the placebo group and 20 drop out, use as the median, the 50th best of the 79 valid scores rather than the 40th.

2. For the mean placebo observation, use LOCF imputation within the placebo group.

3. Also provide the derived dataset used in the above analyses.

If you have any questions, call Paul Z. Balcer, Regulatory Health Project Manager, at 301-796-1173.

Sincerely,

{See appended electronic signature page}

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

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/s/

Bob Rappaport
1/30/2007 04:14:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg, Inc.
450 North Lakeshore Dr.
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D., RAC
Sr. Director, Regulatory Affairs
U.S. Agent for Labopharm Canada, Inc.

Dear Dr. Prokipcak:

We acknowledge receipt on December 19, 2006 of your December 18, 2006 resubmission to your new drug application for Ryzolt (tramadol hydrochloride extended-release) Tablets 100 mg, 200 mg, and 300 mg.

We consider this a complete, class 2 response to our September 28, 2006 action letter. Therefore, the user fee goal date is June 19, 2007.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

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

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/s/

Parinda Jani
1/10/2007 03:00:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm, Inc.
Attention: Robert A. Dormer
Counsel for Labopharm, Inc.
Hyman, Phelps & McNamara
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Dormer:

We refer to the New Drug Application (NDA) submitted by Labopharm, Inc., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) extended-release tablets.

Your December 19, 2006, request for formal dispute resolution, received on December 19, 2006, concerned the approvable action taken by the Division of Anesthesia, Analgesia and Rheumatology (DAARP) on September 28, 2006. Specifically, you contend that DAARP failed to comply with the terms of a Special Protocol Assessment and agreed upon statistical analysis plan by requiring at least one adequate and well-controlled trial.

We also refer to your submission December 18, 2006, received December 19, 2006, which constitutes a complete response to the September 28, 2006, approvable letter. The submission includes a reanalysis of the data from study MDT3-005 that is intended to address the deficiency that is the subject of your appeal.

If DAARP determines that the reanalysis submitted in your complete response is appropriate, this appeal will be unnecessary. Therefore, because you are engaged in another proceeding on this matter, we do not accept your request for formal dispute resolution at this time.

If you have any questions, call Kim Colangelo, Formal Dispute Resolution Project Manager, at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

Kim M. Colangelo
Formal Dispute Resolution Project Manager
Associate Director for Regulatory Affairs
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Kim Colangelo
1/10/2007 11:12:42 AM