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:

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

We also refer to the meeting between representatives of your firm and the FDA on November 27, 2006. The purpose of the meeting was to discuss your response to the Agency's Approvable Letter dated September 28, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Memorandum of Teleconference Minutes

MEETING DATE: Monday, November 27, 2006

TIME: 2:30 p.m. - 3:30 p.m. (EST)

LOCATION: FDA, White Oak, Conference Rm #1417,
10903 New Hampshire Ave, Silver Spring, MD 20993-0002

APPLICATION: NDA 21-745 Ryzolt (tramadol hydrochloride extended-release tablets) 100 mg, 200 mg, and 300 mg

INDICATION: Management of moderate to moderately severe pain

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

TYPE OF MEETING: End of Review Conference (21 CFR 314.102(d))

MEETING CHAIR: Sharon Hertz, M.D.

MEETING RECORDER: Paul Z. Balcer

FDA Attendees

Name	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, M.D.	Deputy Director (Pain Team)
Mwango Kashoki, M.D., M.P.H	Medical Team Leader (Pain Team)
Jin Chen, M.D., Ph.D.	Clinical Reviewer
Thomas Permutt, Ph.D.	Director (Acting), Office of Biostatistics
Dionne Price, Ph.D.	Team Leader (Acting), Office of Biostatistics
Yongman Kim, Ph.D.	Biostatistics Reviewer
Lei K. Zhang, Ph.D.	Clinical Pharmacology Reviewer
Elizabeth Dickinson, J.D.	Office of the Chief Counsel
Janice Weiner, J.D., M.P.H.	Office of Regulatory Policy
Paul Z. Balcer	Regulatory Health Project Manager
Kathleen Davies, M.S.	Regulatory Health Project Manager

Labopharm Canada, Inc./CanReg, Inc. Attendees

Name	Title
James Howard-Tripp	President and CEO
Sylvie Bouchard, M.D., Ph.D.	Vice President, Clinical Development and Regulatory Affairs
Lynda Covello	General Counsel & Corporate Secretary
Robert A. Dormer	Regulatory Counsel; Hyman, Phelps & McNamara, P.C.
Rosane Ouellett, B.Sc. Pharm.	Director, Regulatory Affairs
Anne Tomalin, B.A., B.Sc.	Consultant to Labopahrm, CanReg, Inc.
David Karhu, B.Sc.	Director, Pharmacokinetics
Anthony Santopolo, M.D.	Vice President, Regulatory Affairs, Purdue Pharma

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After brief introductions, the Sponsor presented the Division with the specific agenda items for discussion, namely: the consideration of alternative imputation strategies, additional analyses of efficacy such as the Time Weighted Average (TWA) analysis, and how Labopharm can proceed with the application. The Sponsor's questions and the Division's responses were then addressed.

Sponsor's Comment 2.0: It is contradictory for the Agency in its Action letter to have characterized the method of imputation used in the primary analysis of study MDT3-005 as "inappropriate" when it had formally agreed to this method under the SPA.

Sponsor's Comment 3.0: Given that Labopharm conducted the study according to the approved protocol and analyzed the results according to the approved SAP and that no notification was given to Labopharm by the Agency of a need to change the SAP because of unrecognized public health concerns, we believe that the Agency has failed to comply with the Special Protocol Assessment.

Sponsor's Comment 6.0: The Responder Analysis the Agency performed post hoc differs from the method formally agreed to under the SAP and has led the Agency to an incorrect decision which would not have occurred, had the SPA been adhered to.

FDA Response:

Under the Special Protocol Assessment, the Division agreed that the Last Observation Carried Forward (LOCF) imputation method could be used in the primary efficacy analysis of the study. However, the Division also required that the LOCF-based results be confirmed by sensitivity analyses. Labopharm chose the Baseline Observation Carried

Forward (BOCF) method and a responder analysis as the sensitivity analyses. The BOCF analysis failed to support LOCF results, and this was verified by our own analysis.

It appears that there was a misunderstanding between the Division and Labopharm as to how the responder analysis would be performed. The statistical analysis plan specified a responder analysis in which response was defined as at least a 2-point improvement in pain intensity score from baseline. The Division understood that the analysis would compare the proportion of responders at the end of the trial, and not at any point during the trial. The *post hoc* responder analyses described in the study report were 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, therefore, conducted its own comparison of treatment response using a cumulative distribution curve, and this showed no difference between Ryzolt and placebo.

Since the LOCF method was not supported by either of your sensitivity analyses, nor by additional analyses conducted by the Division, we concluded that the results of the primary efficacy analysis using the LOCF method was not sufficient to support a finding of efficacy.

Discussion:

The Sponsor noted that the Division's responses indicate that the alternative statistical analyses described in the meeting package will be considered; however, the purpose of the SPA was to "fix in time" an agreement on the design and endpoints for study MDT3-005. The Division responded that during the discussions regarding the SPA, the Division made it clear that the primary efficacy analysis with LOCF imputation would not be acceptable if it were not supported by other imputation methods. Thus, although there was agreement on the protocol under a SPA, there is no agreement that the submitted results fulfilled the conditions of the SPA.

The Sponsor discussed two broad classes of alternatives to LOCF. One class involved imputing what might have happened to dropouts if they had continued the assigned treatment. The other class involved imputing what did happen but was not observed, taking into account that the patients did discontinue treatment. The Division was more interested in the second class. The Sponsor described an analysis in which a typical placebo score, rather than a baseline score, was imputed, as an example of the second class. The Division believed this analysis might be very useful. Care was needed, however, in defining a typical placebo score, as the placebo group was also subject to informative censoring.

Sponsor's Comment 4.0: BOCF as an alternative method of imputation on the PI-NRS at the end of study does not take into consideration the large decline in the average pain score between Visits 4 (Baseline) and 5 (Week 2), seen in both groups, and for over 90% of subjects randomized, and consequently underestimates the true treatment effect.

FDA Response:

We acknowledge the improvement in mean pain scores for both the placebo and Ryzolt groups, and the numerically greater improvement in pain scores for the Ryzolt group

compared to placebo at Week 2 (Labopharm's Table 1, appended). However, for this product that is intended to treat chronic pain, it is important that significant differences from baseline and between treatment groups be observed over the entire duration of treatment and also at the end of treatment. The submitted table suggests that a treatment effect occurred only at Week 2 of the study

Sponsor's Comment 5.0: It is inaccurate for the Agency to have characterized Ryzolt as a product that only works in those patients who cannot tolerate it.

FDA Response:

The comment paraphrases remarks that the Division made during our teleconference on October 20, 2006, and referred to our interpretation of the efficacy findings after imputation of missing data due to dropouts. The Division explained that imputation of "good" scores for those patients who dropped out due to intolerable adverse events (i.e. imputation with LOCF) resulted in positive efficacy results; however these results were primarily attributable to patients who could not tolerate study treatment.

Sponsor's Comment 6.1. Time Weighted Average (TWA) is a method of analysis requested by the FDA. The use of TWA analysis accounts for the fluctuations in time observed with the natural history of osteoarthritis (OA) thereby providing information on the total benefit throughout the study. The TWA analysis supports the efficacy of Ryzolt: it shows statistical significance regardless of whether the method of imputation used is LOCF or BOCF.

Sponsor's Response 6.2 All of the sensitivity analyses, with the exception of BOCF, demonstrated consistency in both the direction and magnitude of the treatment effect. Three of the methods (LOnStCF, Placebo Mean and Placebo Median) demonstrated statistical significance at the 0.05 level supporting the primary analysis using LOCF, and these findings did not change substantially when the "effective sample size" was decreased to account for the amount of missing data.

FDA Response:

The TWA analysis, as well as the analyses with LOnStCF, Placebo Mean and Placebo Median imputation merit further consideration. However, there was insufficient information provided in the meeting package for the division to fully understand how the additional analyses were performed. The Division encourages you to include these analyses upon resubmission of your NDA. Include in the resubmission all relevant literature or theory for each method, as well as information detailing implementation of these methods. You may also submit derived data and programs to expedite the statistical review.

Discussion:

The Sponsor explained that the objective of the TWA is to get the sense of robustness of the efficacy and to see real drug effect. BOCF imputation, which assigns unfavorable values for a patient who drops out of the study, focuses on patient status as the end of the study thereby

limiting the 'power' of the study. TWA accounts for the overall experience of the patient during the trial, whether or not they are on treatment. The Division agreed that the TWA might be a good way to summarize the experience of a patient over 12 weeks, but noted that the 12-week experience is itself a surrogate for outcomes over a longer term. Patients who do not tolerate the treatment for 12 weeks cannot be expected to benefit from it in the long term. The Sponsor stated that the frequency of patient dropout observed during the trial would be much less in clinical practice where dosing would be based on tolerability and effect. The Division noted that the trials did not investigate the effects in such a setting. Accordingly, for a trial of only 12 weeks, the Division believes the end-of-study analysis is more relevant than the time weighed average.

Sponsor's Comment 7.0: The assertion that plasma tramadol levels are below those of Ultram® for a "significant portion of time" is not supported by the data. Mean plasma tramadol concentrations following administration of Ryzolt were maintained above the lowest mean concentration attained for Ultram® for 83% of the dosing interval (from within 1 hour post-dose until at least 20 hours post-dose following once-daily administration of 200 mg). Mean plasma tramadol concentrations following administration of Ultram ER® were maintained above the lowest mean concentration attained for Ultram® for only 70% of the dosing interval (from approximately 5 hours post-dose until approximately 22 hours post-dose following once-daily administration of 200 mg).

FDA Response:

To our knowledge, a pharmacokinetic/pharmacodynamic relationship supporting a minimum therapeutic level for tramadol is not well-established, and the 100 ng/mL value cited in the literature has not been validated.

While your data suggest that Ultram ER had mean plasma tramadol concentrations above the lowest mean concentration attained for Ultram over a shorter period than Ryzolt, efficacy of Ultram ER was demonstrated in clinical trials. The clinical finding of efficacy supersedes any pharmacokinetic information regarding the percentage of time the mean plasma concentration of tramadol was below the C_{min}.

Discussion:

The Division commented that the issue for this product is not whether tramadol is efficatious, but whether the Ryzolt formulation is suitable for once-daily chronic dosing. That is, does this new formulation of a known active moiety serve as an effective treatment for chronic pain.

SPONSOR'S QUESTIONS

Sponsor's 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. Given that the FDC Act and the Guidance to Industry provide that the Agency is bound by the SPA, will the Agency reconsider its

position on the deficiencies identified in the review of the NDA? If so, what is the timeframe within which this will occur?

Sponsor's Question #2: Does the Agency agree that the alternative methods of imputation and analysis provided by Labopharm are sufficient to regard MDT3-005 as a positive study? If so, is the Agency willing to reconsider its position on the deficiencies identified in the review of the NDA? What is the timeframe within which this modification could be made?

FDA Response:

See above responses.

Discussion:

The Sponsor asked the Division for advice on how to move forward. The Division responded that the Sponsor should resubmit the NDA, including the additional statistical analyses described in the meeting package. The Division recommended that as much written detail as possible for the statistical analyses be included in the NDA. The Division welcomed the Sponsor to seek guidance regarding data presentation prior to submission of the application. Sponsor and the Division agreed that it would be beneficial to arrange a discussion between the two statistical teams, prior to resubmission.

The Sponsor inquired whether the resubmission would be a Class 1 or Class 2 application. The Sponsor was informed 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.

ACTION ITEMS

The Sponsor is to reevaluate the information provided by the Division and continue the discussions on their proposed statistical analysis plan.

Attachment:
Sponsor's Table (p.6 of the 11/7/2006 meeting package)

Table 1 Mean and Changes for each study visit from Baseline (Visit 4) to the End of Study (Visit 9)

Visit	Mean		Mean Change	
	Placebo	Ryzolt	Placebo	Ryzolt
4 Baseline	7.2 (0.11) N = 214	7.2 (0.08) N = 431		
5 Week 2	5.3 (0.15) N = 196 (92%)	4.4 (0.11) N = 395 (92%)	-1.9 (0.15)	-2.8 (0.12)
6 Week 3	5.0 (0.15) N = 183 (86%)	4.2 (0.12) N = 358 (83%)	-0.1 (0.13)	-0,2 (0.10)
7 Week 6	4.5 (0.17) N = 172 (80%)	4.0 (0.12) N = 341 (79%)	-0.5 (0.13)	-0.2 (0.10)
8 Week 9	4.4 (0.18) N = 167 (78%)	3.9 (0.13) N = 331 (77%)	-0.1 (0.13)	-0.1 (0.08)
9 Week 12	4.3 (0.17) N = 167 (78%)	4.0 (0.13) N = 328 (76%)	-0.1 (0.12)	-0.1 (0.09)

Denominators for percents are numbers of subjects with data at Visit 4.

Values in parentheses are standard errors.

Mean change denotes the average of the changes between visits. A negative mean change reflects an improvement in the PI-NRS.

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/s/

Paul Balcer
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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:

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

We also refer to the meeting between representatives of your firm and the FDA on October 20, 2006. The purpose of the meeting was to discuss the September 28, 2006 approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Memorandum of Teleconference Minutes

MEETING DATE: Friday, October 20, 2006

TIME: 3:30 p.m. - 4:30 p.m. (EST)

LOCATION: Teleconference, FDA, White Oak, Conference Rm #3270, 10903 New Hampshire Ave, Silver Spring, MD 20993-0002

APPLICATION (DRUG): NDA 21-745 Ryzolt (tramadol HCl ER) tablets.

INDICATION: Management of moderate to moderately severe pain

SPONSOR: Labopharm Canada, Inc. (CanReg, Inc., U.S. Representative)

TYPE OF MEETING: Type A, guidance

MEETING CHAIR: Sharon Hertz, M.D.

MEETING RECORDER: Paul Z. Balcer, P.M.

MEETING OBJECTIVE: Discussion of the September 28, 2006 approvable letter

BACKGROUND:
Meeting request: October 2, 2006, received October 4, 2006
Meeting package: Included in the meeting request.

A type A meeting was granted on October 18, 2006.

FDA Attendees

Name	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz, M.D.	Deputy Director (Pain Team)
Mwango Kashoki, M.D., M.P.H.	Clinical Team Leader (Pain)
Jin Chen, M.D., Ph.D.	Clinical Reviewer
Thomas Permutt, Ph.D.	Biostatistics, Acting Director
Dionne Price, Ph.D.	Biostatistics Acting Team Leader
Yongman Kim, Ph.D.	Biostatistics Reviewer
Ali Al Hakim, Ph.D.	PAL Chemistry Reviewer
Sue-Ching Lin, Ph.D.	Chemistry Reviewer
Ted Chang, Ph.D.	Chemistry Reviewer
Elizabeth Dickinson, J.D.	Office of Chief Counsel
Janice Weiner, J.D.	Office of Regulatory Policy

Paul Z. Balcer	Regulatory Health Project Manager
Kathleen Davies, M.S.	Regulatory Health Project Manager

Labopharm Canada, Inc./CanReg, Inc. Attendees

James Howard-Tripp	CEO, Labopharm
Lynda Covello	General Counsil & Corporate, Labopharm
Rosane Ouellet	Director Regulatory Affairs, Labopharm
Sylvie Bouchard	V.P. Clinical and Regulatory Affairs, Labopharm
Robert A. Dormer	Consultant, Hyman, Phelps & McNamara
Anne Tomalin	President, CanReg, Inc.
Becky Prokipcak	Sr. Director Regulatory Affairs, CanReg Inc
Anthony Santopolo	Vice-President, Regulatory Affairs, Purdue Pharma

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Meeting Objective: The purpose of the meeting was to discuss the September 28, 2006 approvable letter, specifically the following comment:

"You have not provided substantial evidence that Ryzolt is effective for your proposed indication of the management of moderate to moderately severe pain. Your conclusion that efficacy has been demonstrated in studies MDT3-003 and MDT3-005 depends on the use of a last observation carried forward (LOCF) imputation methodology for patients who dropped out of the studies. We consider this method of imputing missing data inappropriate, and efficacy was not confirmed when other methods, such as baseline observation carried forward (BOCF) or continuous responder analysis (of the patient's status at the end of the study) were employed. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial. Ryzolt produced at your commercial manufacturing site should be used in future clinical trials."

Background:
On September 28, 2006 the Agency forwarded the approvable letter to Labopharm Canada, Inc. The sponsor responded with questions regarding the Agency's sensitivity analyses of the primary method of imputation for missing data, LOCF, that was used for study MDT3-005. To facilitate the October 20 discussion, the division forwarded the Agency's continuous responder analysis for study MDT03-005 to the Sponsor prior to the meeting (see attached).

Presented below are Agency comments related to the sponsor's background material and responses to questions in the meeting request submission. The sponsor's questions are listed in *italics* with the discussion that took place at the meeting in normal text.

1. *Study MDT3-005 was conducted under a Special Protocol Assessment agreement whereby both the protocol and the Statistical Analysis Plan were agreed by the FDA and Labopharm before the study was conducted and results analyzed.*

2. *Has the FDA relied on a different sensitivity analysis in arriving at its conclusion than that which was agreed to under the SPA? Please provide further clarification, details on the method of analysis upon which you relied in reaching your conclusion, and the results that you obtained.*

3. *Labopharm wishes to better understand the discrepancy between the Labopharm analysis and that conducted by the FDA.*

Discussion:

The Division agreed that study MDT3-005 was carried out under a Special Protocol Agreement and that the primary analysis by LOCF appeared to show efficacy. However, as communicated previously, primary analysis employing LOCF as the imputation methodology for missing data would not be sufficient unless confirmed by sensitivity analyses. Although some sensitivity analyses performed by the applicant appeared to confirm the efficacy results, these analyses all shared the common flaw of attributing good scores to patients who were unable to tolerate Ryzolt and subsequently discontinued treatment. Indeed, essentially all the efficacy of the drug in these analyses was attributable to patients who dropped out. If such a drug were approved, it would present insurmountable problems in labeling as the patient population for which the drug was effective appears to be the population which could not tolerate it.

The Division emphasized that it has been consistent in its advice to sponsors regarding preferred imputation strategies for trials of analgesic products. In this case, although there was agreement on the protocol and the planned analyses, including incorporation of sensitivity analyses, the Division does not agree with Labopharm as to the interpretation of the resultant data.

The Sponsor asked for further explanation regarding why Ryzolt cannot be approved on the basis of intolerability, since other tramadol products with a similar adverse event profile have previously been approved. The Division responded that because Ryzolt has a different pharmacokinetic profile from other FDA-approved tramadol products, Labopharm had to demonstrate efficacy of Ryzolt. Based on the study results, efficacy was not shown.

The Sponsor stated that Labopharm would consider all of the Division's comments and provide a response. The Sponsor asked the Division how Labopharm could proceed with development of Ryzolt. The Division suggested that the Sponsor re-evaluate the pharmacokinetics and dosing regimen of the

product, as well as consider assessment of efficacy in a different pain population and use of alternative imputation strategies for missing data.

ACTION ITEMS

The Sponsor is to reevaluate the information provided by the Division and continue the discussions at a later date.

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/s/

Paul Balcer
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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:

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

We also refer to your October 11, 2006, correspondence, received October 12, 2006, requesting a meeting to discuss the plans to address deficiencies in the September 28, 2006 approvable letter.

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 21, 2006**
Time: **10:30 a.m. – 11:30 a.m. (EST)**
Location: **FDA, White Oak, Conference Rm. #1313**
10903 New Hampshire, Silver Spring, M.D. 20993-0002

CDER participants: Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia and Rheumatology Products
Sharon Hertz M.D., Deputy Director
Mwango Kashoki, M.D., M.P.H., Team Leader
Jin Chen, M.D., Ph.D., Medical Officer
Thomas Permutt, Ph.D., Director (Acting), Office of Biostatics
Dionne Price, Ph.D., Team Leader (Acting), Office of Biostatistics
Yongman Kim, Ph.D., Biostatistics Reviewer
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Lei K. Zhang, Ph.D., Clinical Pharmacology Reviewer
Paul Z. Balcer, Regulatory Health Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at paul.balcer@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: Paul Z. Balcer, 796-1173; the division secretary, 796-1169.

Provide the background information for this meeting (three copies to the NDA and ten desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 7, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
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/

Paul Balcer
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Paul Balcer
10/18/2006 03:54:36 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

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Sr. Director, Regulatory Affairs
U.S. Agent for Labopharm Canada, Inc.

Dear Dr. Prokipcak:

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We also refer to your October 2, 2006, correspondence, received October 4, 2006, requesting a teleconference to discuss the September 28, 2006 approvable letter.

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:	**October 20, 2006**
Time:	**3:30 p.m. – 4:30 p.m. (EST)**
Phone Arrangements:	**FDA will call Labopharm Canada with a prearranged phone number.**

CDER Participants: **Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia and Rheumatology Products**
Sharon Hertz M.D., Deputy Director
Mwango Kashoki, M.D., M.P.H., Team Leader
Jin Chen, M.D., Ph.D., Medical Officer
Thomas Permutt, Ph.D., Director (Acting), Office of Biostatics
Dionne Price, Ph.D., Team Leader (Acting), Office of Biostatistics
Yongman Kim, Ph.D., Biostatistics Reviewer
Janice Weiner, Office of Chief Counsel
Paul Z. Balcer, Regulatory Health Project Manager

The background information for this meeting was provided with the meeting request, therefore no additional material is expected prior to the meeting.

If you have any questions, call me, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
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/

Paul Balcer
10/18/2006 03:34:08 PM

From: Balcer, Paul
Sent: Wednesday, October 04, 2006 3:18 PM
To: 'Becky Prokipcak PhD, RAC'
Cc: Stradley, Sara
Subject: NDA 21-745 Ryzolt (tramadol hydrochloride extended release) - Teleconference follow up.

Dear Dr. Prokipcak,

Thank you for leaving me the voice mails. The Division would prefer to keep the October 20, 2006 meeting as a teleconference and continue our discussions at a face-to-face meeting at a later date. The Division believes that the teleconference would be productive as an initial step in discussing the content of the approvable letter and possible path(s) to move forward with addressing the deficiencies.

Best regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
10903 New Hampshire Ave.
Bldg. 22 Rm. 3145
Silver Spring, MD 20993-0002
Tel.: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
10/4/2006 03:47:28 PM
CSO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	September 28, 2006
DRUG:	Ryzolt (tramadol HCl extended-release tablets), 100 mg, 200 mg and 300 mg
NDA:	21-745
SPONSOR:	Labopharm Canada Inc.
INDICATION:	For the management of moderate to moderately severe pain

Labopharm Canada Inc. has submitted NDA 21-745 in support of marketing approval for Ryzolt, for the management of moderate to moderately severe pain. This product is an extended-release tablet formulation of tramadol HCl that was studied in dosage strengths of 100, 200 and 300 mg. The Ryzolt tablet is comprised of a dual-matrix delivery system with an outer layer that is designed to release tramadol in an extended manner, but at a faster rate than the core layer. This application was submitted through the approval pathway described by section 505(b)(2) of the Food, Drugs and Cosmetics Act, and the applicant has relied upon the Agency's prior finding of safety and effectiveness of Ultram for some portions of the submission. Labopharm has provided a patent certification to Ultram's listed patent and has performed a relative bioavailability study of Ryzolt compared to Ultram. The Agency has determined that this product has sufficiently different biopharmaceutical features from Ultram ER, another extended-release tramadol product, to allow filing and review as a 505(b)(2) application.

The CMC sections of this application were reviewed by Sue-Ching Lin, M.S., R.Ph. and Ted Chang, Ph.D. The Clinical Pharmacology and Biopharmaceutics section was reviewed by Lei Zhang, Ph.D. The Pharmacology and Toxicology review was completed by Asoke Mukherjee, Ph.D. The clinical safety and efficacy review was completed by Jin Chen, M.D., Ph.D. A statistical review and evaluation was completed by Yongman Kim, Ph.D. Mwango Kashoki, M.D. provided a secondary review of the application

summarizing the clinical and statistical findings and the clinically relevant aspects of the findings from the other disciplines' reviews. Consultation on this application was obtained from the Controlled Substances Staff, the Office of Surveillance and Epidemiology, and the Division of Drug Marketing, Advertisement and Communications. This memo will briefly review the findings of the review team.

Efficacy:

The sponsor submitted the results of three adequate and well-controlled trials in their application. Two of these trials, Study MDT3-003 (003) and Study MDT3-005 (005) were submitted in support of their claim that the product is effective. Study MDT3-002 (002) was identical in design to Study 003 and was included in the application, although the sponsor acknowledged that it failed to demonstrate efficacy.

Study 003

This study was a parallel-design, randomized, double-blind, placebo-controlled, multi-center trial that compared Ryzolt 100 mg, 200 mg and 300 mg to placebo, in adults with osteoarthritis of the knee and a minimal pain intensity score of greater than 150 mm on the WOMAC Pain Subscale. The primary outcome measure was the percent change in the WOMAC Pain Subscale score from baseline to the end of the study at Week 12. Secondary outcome measures included:

- The percent change in the WOMAC Physical Function score at Week 12
- The average Physician Global Rating of Pain Relief over the maintenance phase
- The average Patient Global Rating of Pain over the maintenance phase; and
- The 24-Hour VAS Pain Questionnaire at each visit during the maintenance phase

The sponsor's analysis of the primary outcome employed a LOCF imputation methodology and found that only the 300-mg dose demonstrated a statistically significant treatment effect compared to placebo. The sponsor also analyzed the data employing a BOCF imputation methodology which demonstrated no statistically significant treatment effect for any dose of Ryzolt compared to placebo. Dr. Kim's analyses confirmed these results. Dr. Kashoki's table (page 17 of her review) summarizes these data and is reproduced below:

Endpoint	Tramadol OAD			PBO
	100mg	200mg	300mg	
LOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	122.3	123.4	143.3	99.5
% change in mean pain intensity from baseline to wk 12	41.6%	42.8%	46.0%	32.3%
Difference in % change (Tramadol OAD vs. PBO); p-value	9.5 0.0933	10.8 0.0504	13.4 0.0162	-
BOCF imputation - Applicant				
Difference in % change (Tramadol OAD vs. PBO); p-value	6.44% 0.1910	2.35% 0.6292	0.00% 0.9997	-
BOCF imputation - FDA				
% change in mean pain intensity from baseline to wk 12	36%	32%	31%	29%
Difference in % change (Tramadol OAD vs. PBO); p-value	7% 0.1682	3% 0.4843	2% 0.7064	-

The sponsor also performed a responder analysis and looked at 10%, 30% and 50% improvement. They found that the 200-mg dose demonstrated a statistically significant effect at 10% and 30%, and the 300-mg dose demonstrated a statistically significant effect at 30% and 50%, but not 10%. The sponsor's analysis inappropriately included LOCF imputation. As patients who drop out are treatment failures and, therefore, should be counted as nonresponders, imputation by LOCF is neither a necessary nor correct approach in a responder analysis of a response defined by a single, simple metric, e.g., pain intensity score on the WOMAC Pain Scale. Dr. Kim reanalyzed the data using a continuous responder analysis and compared the resultant curves from the treatment and placebo groups with a van der Waerden test. No statistically significant separation in the curves was demonstrated.

Analyses of the secondary outcome measures using a BOCF imputation methodology were performed by the review team and no statistically significant treatment effects were found for any of the doses of Ryzolt compared to placebo.

Study 005

This study was a parallel-design, randomized, double-blind, placebo-controlled, multi-center trial that compared Ryzolt to placebo, in adults with osteoarthritis of the knee and a minimal pain intensity score of greater than or equal to 4 on an 11-point Pain Intensity Numerical Rating Scale. The trial employed an initial open-label phase during which subjects were titrated to individual Ryzolt doses based on optimal efficacy and tolerability. Thirty-five percent of the subjects dropped out during the open-label phase,

22% due to adverse events (AEs) and 3% due to Lack of Efficacy. The remaining subjects underwent washout followed by randomization to either their previously demonstrated optimal dose or placebo. The subjects were titrated to these doses over two weeks and then maintained on the doses for 12 weeks. The primary outcome measure was the percent change in the group mean Pain Intensity score from baseline (defined as the end of the washout period) to the end of the study at Week 12. Secondary outcome measures included:

- The percent change in the WOMAC Pain Score at Week 12
- The percent change in the WOMAC Physical Function score at Week 12; and
- The Patient and Physician Global Impression of Change at Week 12

Employing the LOCF imputation methodology, the sponsor found that there was a statistically significant treatment effect for the Ryzolt group compared to the placebo group. However, a reanalysis employing the BOCF imputation methodology found no statistically significant treatment effect. Dr. Kashoki's table (page 14 of her review) summarizes these data and is reproduced below:

Endpoint	Tramadol OAD	Placebo	Difference	p-value
LOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	2.4 ± 2.4	2.9 ± 2.5	- 0.48	0.0157
Percent change in mean pain intensity from baseline to wk 12	-40.3%	-33.3	7.3%	.
BOCF imputation				
Absolute change in mean pain intensity from baseline to wk 12	4.8 ± 2.6	25.0 ± 2.5	- 0.25	0.2135

The sponsor also conducted a responder analysis which they interpreted as supportive of efficacy. However, when Dr. Kim performed a continuous responder analysis, he found that, employing a van der Waerden test, there was no statistically significant separation between the Ryzolt and placebo curves. The secondary outcome measures were also not supportive of efficacy for Ryzolt.

Study 002

The data from this study are summarized in Dr. Kashoki's table (page 21 of her review) and demonstrate the absence of a statistically significant treatment effect, even when the LOCF imputation methodology is employed. That table is reproduced below:

Endpoint	Tramadol OAD			PBO
	100mg	200mg	300mg	
LOCF imputation				
Absolute change in mean WOMAC pain from baseline to wk 12	107.6	117.4	129.3	112.3
% change in mean WOMAC pain from baseline to wk 12	36%	37%	41%	38%
Difference in % change (Tramadol OAD vs. PBO); p-value	-2% 0.72	-1.5% 0.77	2.9 0.56	-

Clinical Safety:

Two deaths occurred in subjects treated with Ryzolt. A 67-year old woman died after suffering an ischemic cerebral infarction. She had been taking Ryzolt 400 mg for 36 days. However, the subject had significant risk factors for stroke including cardiovascular disease and hyperlipidemia, and she was on multiple medications. Another 67-year old woman with a history of HTN had taken Ryzolt 100 mg for two months when she suffered a myocardial infarction. She had been transferred to an extended-care facility after heel surgery and became agitated four days later. She was then transferred to another medical center and diagnosed as having Bipolar Disorder. She collapsed and died six days after admission to the second medical center. It is unclear whether the patient stopped taking the study medication during or after the surgical procedure. Dr. Chen notes that the patient's agitation could have been due to serotonin syndrome, a know AE associated with tramadol exposure.

The serious adverse events, adverse events resulting in discontinuation and common adverse events were all AEs known to occur in patients exposed to tramadol, and did not occur with greater frequency than would be expected.

Clinical Pharmacology and Biopharmaceutics:

Ryzolt has a median T_{max} of 4 hours. Lower plasma levels than Ultram (dosed every 6 hours) were noted during the absorption phase (0 to 3 hours post-dose) and at the terminal phase (18 to 24 hours). This finding indicates that there is a relatively lower plasma level of once-daily dosed Ryzolt compared to Ultram dosed according to the label every 6 hours, over a 9-hour period. This difference may, at least partially, have contributed to the lack efficacy noted for the Ryzolt formulation.

Chemistry, Manufacturing and Controls; Non-Clinical Safety:

The review teams have determined that there were no findings that would preclude approval of this product from a pre-clinical perspective.

Discussion

The sponsor has failed to provide sufficient evidence that Ryzolt is effective when used according to their proposed and studied dosing regimen. While this outcome may have been partially due to the pharmacokinetic profile of Ryzolt, which shows low plasma levels of tramadol (compared to Ultram) during a critical 9-hour window of daily treatment for the osteoarthritis patient population, the study designs may have also contributed to the lack of ability to demonstrate efficacy. Fixed-dose studies of tramadol do not allow patients to adjust to the considerable side effects associated with this drug. The sponsor's interpretation of the efficacy results from Studies 003 and 005 is based on a statistical analysis that employs a LOCF imputation methodology. This methodology is inappropriate for a drug that is meant to primarily treat pain. Patients with pain due to osteoarthritis (and most other chronic medical conditions) do not continue treatment with a medication that they are unable to tolerate due to side effects. These patients will generally switch to an analgesic with a more acceptable tolerability to effectiveness ratio. The sponsor was asked to incorporate sensitivity analyses employing more conservative imputation methodologies into their protocols in discussions with the Division during the development of their Phase 3 clinical program. The Division emphasized the need to clearly demonstrate that a finding of efficacy was not due to an uneven distribution of dropouts and an imputation methodology that maximized efficacy and minimized intolerance.

Although this product does not appear to increase the risks associated with tramadol exposure based on its novel formulation, the inability to demonstrate efficacy in the submitted trials precludes approval of the product at this time. The sponsor will need to perform a new clinical trial that is appropriately designed and that demonstrates a reasonable balance of efficacy and tolerability. It may, indeed, be necessary for the sponsor to reformulate this product to allow a pharmacokinetic profile that provides more consistently adequate plasma levels of tramadol in order to achieve this balance.

Action: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
9/28/2006 05:19:40 PM
MEDICAL OFFICER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY (REVISED)

DATE: 9/21/06

TO: Paul Balcer, Regulatory Project Manager
Jin Chen, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Drug Products

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

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-745

APPLICANT: Labopharm, Inc.

DRUG: Tramadol Contramid OAD

THERAPEUTIC CLASSIFICATION: S

INDICATION: Moderate to Severe Pain

CONSULTATION REQUEST DATE: 8/24/06

PDUFA DATE: 9/28/06

I. BACKGROUND:

Tramadol is a synthetic, centrally acting, narcotic agonist analgesic that has been marketed in the US for pain, as Ultram, since 1995. The suggested dosing regimen for Ultram is 4 times a day (QID). Tramadol Contramid OAD (once-a-day) is a sustained-release formulation. Labopharm, Inc., submitted clinical trials with Tramadol Contramid

OAD to FDA in NDA 21-745, to determine if the sustained-release preparation would improve patient compliance and produce a more consistent absorption rate with enhanced safety and efficacy profiles over the QID dosing.

Protocol MDT3-005 was identified as an important protocol in the NDA. It was a multi-center, double-blind, parallel-design trial to compare the analgesic efficacy of Tramadol OAD versus placebo in subjects with osteoarthritis of the knee. The protocol is entitled: "A Two-Arm Study Comparing the Analgesic Efficacy and Safety of Tramadol HCl Once-a-Day Versus Placebo for the Treatment of Pain due to Osteorarthritis." The primary efficacy endpoint was the Pain Intensity Score at visit 9 (end of study), measured by an 11-point numerical Rating Scale score.

Two clinical sites with large enrollments were selected for inspection. The inspection results are summarized below:

II. RESULTS (by protocol/site):

Name of Investigator	City, State	Protocol	Insp. Date	Date EIR Received	Final Class.
Francis X. Burch, M.D.	San Antonio, TX	MDT3-005	8/21-24/06	9/8/06	NAI
Nicholas J. Messina, M.D.	Mesa, AR	MDT3-005	7/31-8/3/06	9/6/06	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations.

Protocol #MDT3-005

1. Francis X. Burch, San Antonio, Texas

a. What was inspected: Dr. Burch screened 62 subjects and randomized 27. Study records for 20 subjects were reviewed during the inspection. The records audited included source documents, case report forms, efficacy data listings provided by the sponsor, informed consent documents, drug accountability records, and correspondence with the sponsor and IRB.

b. Limitations of inspection: None.

c. General observations/commentary: The inspection revealed the study was conducted adequately. Source data were accurately reported in case report forms, with the exception that one adverse event (subject 436 reported a right side lower back muscle strain at Visit 4) was inadvertently not reported on the corresponding CRF. There were no other unreported adverse events, and all other data, including all efficacy endpoints, were accurately transcribed.

d. Data acceptability/reliability: From the records reviewed, the data from this site appear acceptable and could be used to support an approval decision for the NDA.

2. Nicholas J. Messina III, M.D., Mesa, Arizona

a. What was inspected: Dr. Messina screened 26 subjects and randomized 20 to the open label phase of the protocol; 12 of which continued on to the double-blind phase. Study records for 20 subjects (from both phases) were reviewed during the inspection. The records audited included source documents, case report forms, efficacy data listings provided by the sponsor, informed consent documents, drug accountability records, and correspondence with the sponsor and IRB.

b. Limitations of inspection: None.

c. General observations/commentary: here were no discrepancies between source documents and CRFs. There did not appear to be any indication of under-reporting of adverse events. There was 1 SAE (subject 020/512 - syncope requiring hospitalization) which was appropriately reported to both the sponsor and the IRB.

Two protocol deviations were noted.

1) The protocol stated that subjects who had therapeutic arthroscopy on the target knee within 12 months should be excluded from the study. Subject 023/067 had therapeutic arthroscopy of the target (right) knee in 10/2004 to repair cartilage, but was enrolled in the tramadol study on 7/6/05 (≈9 months later).

2) The protocol stated that subjects must discontinue all analgesic drugs for at least 5 drug half-lives. Subject 023/067 took piroxicam from 5/10/05 to 7/2/05. The washout period (5 drug half-lives) for piroxicam was listed as 11 days, but the subject was administered tramadol on 7/6/05, 4 days later.

d. Data acceptability/reliability: With the exception of the enrollment of subject 023/067, the study appears to have been conducted adequately. We recommend that the Review division consider whether the data for subject 023/067 should be removed from the safety and efficacy evaluation of the study. Otherwise, the remaining data generated by this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

With the possible exception of data for subject 023/067 at the Messina site, the data generated from the studies appear acceptable and could be used to support an approval decision for the NDA.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

Carolanne Currier
9/21/2006 01:04:18 PM
CSO

Constance Lewin
9/21/2006 01:19:57 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 9/20/06

TO: Paul Balcer, Regulatory Project Manager
Jin Chen, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Drug Products

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

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-745

APPLICANT: Labopharm, Inc.

DRUG: Tramadol Contramid OAD

THERAPEUTIC CLASSIFICATION: S

INDICATION: Moderate to Severe Pain

CONSULTATION REQUEST DATE: 8/24/06

PDUFA DATE: 9/28/06

I. BACKGROUND:

Tramadol is a synthetic, centrally acting, narcotic agonist analgesic that has been marketed in the US for pain, as Ultram, since 1995. The suggested dosing regimen for Ultram is 4 times a day (QID). Tramadol Contramid OAD (once-a-day) is a sustained-release formulation. Labopharm, Inc., submitted clinical trials with Tramadol Contramid OAD to FDA in NDA 21-745, to determine if the sustained-release preparation would

d. Data acceptability/reliability: From the records reviewed, the data from this site appear acceptable and could be used to support an approval decision for the NDA.

2. Nicholas J. Messina III, M.D., Mesa, Arizona

a. What was inspected: Dr. Messina screened 26 subjects and randomized 20 to the open label phase of the protocol; 12 of which continued on to the double-blind phase. Study records for 20 subjects (from both phases) were reviewed during the inspection. The records audited included source documents, case report forms, efficacy data listings provided by the sponsor, informed consent documents, drug accountability records, and correspondence with the sponsor and IRB.

b. Limitations of inspection: None.

c. General observations/commentary: here were no discrepancies between source documents and CRFs. There did not appear to be any indication of under-reporting of adverse events. There was 1 SAE (subject 020/512 - syncope requiring hospitalization) which was appropriately reported to both the sponsor and the IRB.

Two protocol deviations were noted.

1) The protocol stated that subjects who had therapeutic arthroscopy on the target knee within 12 months should be excluded from the study. Subject 023/627 had therapeutic arthroscopy of the target (right) knee in 10/2004 to repair cartilage, but was enrolled in the tramadol study on 7/6/05 (≈9 months later).

2) The protocol stated that subjects must discontinue all analgesic drugs for at least 5 drug half-lives. Subject 023/067 took piroxicam from 5/10/05 to 7/2/05. The washout period (5 drug half-lives) for piroxicam was listed as 11 days, but the subject was administered tramadol on 7/6/05, 4 days later.

d. Data acceptability/reliability: With the exception of the enrollment of subject 023/067, the study appears to have been conducted adequately. We recommend that the Review division consider whether the data for subject 023/067 should be removed from the safety and efficacy evaluation of the study. Otherwise, the remaining data generated by this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

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/s/

Carolanne Currier
9/20/2006 07:18:45 AM
CSO

Constance Lewin
9/20/2006 10:23:15 AM
MEDICAL OFFICER

From: Balcer, Paul
Sent: Thursday, May 18, 2006 8:24 AM
To: 'Becky Prokipcak'
Subject: NDA 21-745 Tramadol Contramid OAD - Request for Information - study sites for study MDT3-005.

Importance: High
Sensitivity: Confidential

Follow Up Flag: Reply
Due By: Wednesday, May 24, 2006 5:00 PM
Flag Status: Flagged

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet.

Additionally, please refer to your April 6, 2006 correspondence informing us on the status of the study MDT3-005. We request the following information on this study:

1. Name and location of the study sites.

2. Names, addresses and contact information on the investigators at each study site.

Please provide this information as soon as possible but no later than Wednesday, May 24, 2006.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov <mailto:paul.balcer@fda.hhs.gov>

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/s/

Paul Balcer
9/18/2006 02:48:54 PM
CSO

CDocuments and SettingsbalcerpDesktopNDA21745SPLlabeling051606.txt
MessageFrom: Balcer, Paul
Sent: Tuesday, May 16, 2006 2:47 PM
To: 'Becky Prokipcak'
Subject: NDA 21-745 Tramadol Contramid OAD - SPL labeling - Request for resubmission.

Sensitivity: Confidential

Dear Dr. Prokipcak,

We have reviewed and edited the data elements for the submitted Tramadol SPL. However, the SPL is not valid without its NDA numbers. Please revise the SPL to include the NDC numbers and resubmit for posting on NLM.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
9/18/2006 02:58:17 PM
CSO

From: Balcer, Paul
Sent: Monday, June 19, 2006 9:05 AM
To: 'Becky Prokipcak PhD, RAC'
Cc: 'rouellet@labopharm.com'
Subject: NDA 21-745 (tramadol hydrochloride extended release tablets) - Biostatistics Information Request

Importance: High

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended release tablets, 100, 200 and 300 mg.

We are reviewing the Clinical/Biostatistics module of your submission and have the following comments and information requests:

Provide information whether or not each patient studied belongs to Safety Population, Full Analysis Population, ITT Population, and Per Protocol Population for Studies MDT3-001, -002, and -003. Please provide the above information in SAS transport file.

We request a prompt written response in order to continue our evaluation of your NDA. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
9/18/2006 03:47:06 PM
CSO

From: Balcer, Paul
Sent: Wednesday, July 19, 2006 4:26 PM
To: 'Becky Prokipcak PhD, RAC'
Cc: 'rouellet@labopharm.com'
Subject: NDA 21-745 (tramadol hydrochloride extended release tablets) - CMC Information Request.

Importance: High

Follow Up Flag: Reply
Due By: Wednesday, July 26, 2006 3:30 PM
Flag Status: Flagged
Expires: Friday, September 29, 2006 12:00 AM

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended release tablets, 100, 200 and 300 mg.

We are reviewing the module 3 of your submission and have the following information requests:

The in-process controls (section 3.2.P.3.4) indicate that the acceptance criterion for the average core hardness is ——. Provide the analytical procedure and data demonstrating that the method is robust to measure core hardness at ——— b(4)

Provide a description of the potential for the tablet core to ——, ——— ——— Discuss whether ——— has been observed and if so, how it is detected.

We request a written response no later than Wednesday, July 26, 2006 in order to continue our evaluation of your NDA.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
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Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
9/18/2006 02:09:49 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-745** Supplement # **N/A** Efficacy Supplement Type SE- **N/A**

Proprietary Name: **Tramadol Contramid® OAD**
Established Name: **tramadol hydrochloride extended release**
Strengths: **100, 200 and 300 mg controlled release tablet**

Applicant: **Labopharm Canada, Inc.**
Agent for Applicant (if applicable): **CanReg, Inc.**

Date of Application: **November 25, 2005**
Date of Receipt: **November 28, 2005**
Date clock started after UN:
Date of Filing Meeting: **January 20, 2006**
Filing Date: **January 27, 2006**
Action Goal Date (optional): **September 28, 2006** User Fee Goal Date: **September 28, 2006**

Indication(s) requested: Management of moderate to moderately severe pain

Type of Original NDA:	(b)(1) ☐	(b)(2) ☒
AND (if applicable) Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☒ WND 31DEC08

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐

If yes, explain: **Biovail Laboratories International's NDA 21-692 Ralivia ER, has been granted the three-year non-patent exclusivity. However Biovail has submitted a waiver, granting final approval of the Labopharm's product (see attached letter). The Sponsor claims that their product has a dual-delivery system comprising of IR and a controlled release components of Tramadol.**

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☒

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☒

2. This application is an eNDA or combined paper + eNDA YES ☐
This application is: All electronic ☐ Combined paper + eNDA ☐
This application is in: NDA format ☐ CTD format ☐
Combined NDA and CTD formats ☐

Does the eNDA, follow the guidance?
(http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 3 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☒
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: **64,317**
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **February 25, 2004** NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☐ NO ☒
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☒

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☒ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☒
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: **January 20, 2006**

NDA #: **21-745**

DRUG NAMES: **Tramadol Contramid OAD**

APPLICANT: **Labopharm Canada, Inc.**

BACKGROUND: **The Tramadol Contramid OAD, according to the Sponsor, is a unique controlled-release formulation designed to provide both rapid onset of action and sustained relief of pain over a 24-hour period. This application provides for clinical efficacy, safety and pharmacokinetic data sufficient for bridging to the Ultram ER.**

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: **Sharon Hertz, M.D., Deputy Director, Mwango Kashoki, M.D., Acting Pain Team Leader, Jin Chen, M.D., Medical Officer, Ali Al Hakim, Ph.D., Chemistry Reviewer, Asoke Mukherjee, Ph.D., Pharmacology/Toxicology Reviewer, Thomas Permutt, Ph.D., Biostatistics Team Leader, Yongman Kim, Ph.D., Biostatistics Reviewer.**

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	**Jin Chen, M.D., Ph.D.**
Secondary Medical:	**Mwango Kashoki, M.D., M.P.H.**
Statistical:	**Yongman Kim, Ph.D.**
Pharmacology:	**Asoke Mukherjee, Ph.D.**
Statistical Pharmacology:	
Chemistry:	**Ali Al Hakim, Ph.D., Sue Ching Lin, Ted Chen, Ph.D.**
Environmental Assessment (if needed):	
Biopharmaceutical:	**Lei K. Zhang, Ph.D.**
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	**Paul Z. Balcer**
Other Consults:	**Patricia Beaston, M.D., CSS, Mary Dempsey, ODS/OPSS, DMETS, DDRE, Elaine Hu, Pharm.D., DDMAC**

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Paul Z. Balcer
Regulatory Project Manager, Division of Anesthesia, Analgesia and Rheumatology Products

Appendix A to NDA Regulatory Filing Review

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

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 20-281 Ultram® Tablets

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☒

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☒

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** **are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))**

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s): **This version of tramadol (extended-release) should be considered as a pharmaceutical alternative to the IR products, Ultram ODT (NDA 21-693) and Ultram (NDA 20-281) (Please refer to the definitions in the orange book).**

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☒

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **Labopharm is relaying on cross-referencing with FDA's previous finding of the safety and efficacy of the immediate-release formulation of Ultram in the treatment of moderate to moderately severe pain. Additionally the pharm./tox. data (toxicity of tramadol) is referred to Ultram (NDA 20-281).**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☒

that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☒

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s): ~~6,607,748 B1 Expires: June 29, 2020~~ WMD 31Dec08

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☒ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the

labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s): 6,339,105

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☒ NO ☐

If "Yes," what is the listed drug product(s) NDA 21- *and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*: ~~NDA 21-692~~ NDA 20-281 KNO 31Dec08
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☒ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☒ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
NDA 21-692 (Ultram ER)	001/002/003	NP	09/08/08

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
9/11/2006 12:52:40 PM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO: 22, Mailstop 4447)

DATE RECEIVED: June 12, 2006	**DESIRED COMPLETION DATE:** July 11, 2006	**OSE REVIEW :** 06-0050-3
DATE OF DOCUMENT: May 31, 2006	**PDUFA DATE:** September 28, 2006	

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-530

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

Tramadol Hydrochloride Extended-release Tablets
00 mg, 200 mg, and 300 mg

NDA# 21-745

NDA SPONSOR: Labopharm Canada, Inc.

SAFETY EVALUATOR: Linda M. Wisniewski, RN

DMETS RECOMMENDATIONS:

1. DMETS recommends implementation of the label and labeling revisions outlined in section II of this review in order to minimize user error.

2. Please provide container labels and carton labeling for 90-count [redacted] for review and comment.

b(4)

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
DMETS; WO 22, Mailstop 4447
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: July 14, 2006

NDA#: 21-745

NAME OF DRUG: Tramadol Hydrochloride Extended-release Tablets
100 mg, 200 mg, and 300 mg

NDA HOLDER: Labopharm Canada, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products, for assessment of the revised labels and labeling for Tramadol Hydrochloride Extended-release tablets. The sponsor provided draft container labels and carton labeling for review and comment. DMETS evaluated the proposed proprietary name ——— and Ryzolt in OSE consult #06-0050-2. Both Deflexit and Ryzolt were found unacceptable by the Division of Drug Marketing, Advertising, and Communication. Since the Division concurred with DDMAC, DMETS did not conduct a safety review of the proposed proprietary names. b(4)

PRODUCT INFORMATION

Tramadol Hydrochloride Extended-release tablets are a once daily centrally acting analgesic comprised of a dual-matrix delivery system which controls the release of tramadol hydrochloride providing both immediate-release and extended-release characteristics. Tramadol Hydrochloride is indicated for the management of moderate to moderately severe pain. Tramadol Hydrochloride should be taken once a day and be swallowed whole with liquid and not split, chewed, dissolved, or crushed. Treatment should be initiated at 100 mg/day with daily doses titrated by 100 mg/day increments every two days to achieve a balance between adequate pain control and tolerability for the individual patient. For patients requiring a 300 mg daily dose, titration should take at least four days. The maximum recommended dose is 300 mg.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In review of the container labels, carton and insert labeling of Tramadol Hydrochloride, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of improvement, which might minimize potential user error.

A. CONTAINER LABEL (30-count)

1. The established name for this product is Tramadol Hydrochloride Extended-release tablets. Revise for accordingly.

2. Ensure that the established name is at least ½ the size of the proprietary name. See 21 CFR 201.10(g)(2).

3. Relocate the product strength to appear immediately following the established name.

4. We note that the blue colors used for the boxing of the 200 mg and 300 mg strengths are almost identical. Additionally, the dark blue font on the blue background of these two strengths is difficult to read. Revise the colors to provide greater contrast and for greater readability and differentiation between strengths.

5. Decrease the prominence of the net quantity.

B. INSERT LABELING

1. See GENERAL COMMENT A1.

2. The HOW SUPPLIED section of the insert labeling refers to 90-count. [redacted], however, these labels were not supplied for review at this time. b(4)

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

/s/

Linda Wisniewski
9/1/2006 02:30:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/1/2006 02:40:41 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her absence

From: Balcer, Paul

Sent: Tuesday, August 15, 2006 9:56 AM

To: 'Becky Prokipcak PhD, RAC'

Cc: 'nbrufatto@canreginc.com'; 'rouellet@labopharm.com'; Stradley, Sara

Subject: NDA 21-745 (tramadol hydrochloride extended release) tablet - Clinical Information Request.

Importance: High
Sensitivity: Confidential

Dear Dr. Prokipcak,

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended release tablets, 100, 200 and 300 mg. We are reviewing the module 5 of your submission and have the following information request:

Please provide us with the CRFs of dropouts for all six Phase III trials.

We request a prompt written response in order to continue our evaluation of your NDA. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
8/15/2006 10:05:39 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

INFORMATION REQUEST LETTER

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

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

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 (tramadol hydrochloride extended release) 100, 200 and 300 mg tablets.

We also refer to your submission dated May 31, 2006.

The Division of the Drug Marketing, Advertising and Communications (DDMAC) are reviewing your submission and has the following comments on your proprietary names [redacted] and Ryzolt.

1. [redacted]

2. The proposed trade name Ryzolt is unacceptable because it overstates the effectiveness of the drug product. Depending on the pronunciation, the proposed trade name Ryzolt suggests a guaranteed favorable or concrete outcome (pain relief) for the typical patient taking tramadol, thus creating an unrealistic expectation for patients and healthcare providers.

Please note that 21 CFR 201.10(c)(3) states that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(6)(i)]."

We recommend that you submit an alternative proprietary name(s). We request a prompt written response in order to continue our evaluation of your NDA.

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

Sincerely,

{See appended electronic signature page}

Sara Stradley, M.S.
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
7/26/2006 09:20:33 AM

From: Balcer, Paul

Sent: Wednesday, June 21, 2006 2:53 PM

To: 'Becky Prokipcak PhD, RAC'

Cc: 'rouellet@labopharm.com'

Subject: NDA 21-745 (tramadol hydrochloride extended release tablets) - Biostatistics Information Request

Importance: High

Expires: Thursday, September 28, 2006 5:00 PM

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended release tablets, 100, 200 and 300 mg.

We are reviewing the module 5 of your submission and have the following comments and information requests:

We are unable to match the responder analyses for Study 005 conducted by Labopharm. Our analysis does not show the statistical significance shown by the Sponsor after following their algorithm.

In Tables 11.4.1.1.3.1-1 and 14.2-10 of the study report, the denominator of responder proportion is less than the number of subjects in FAS (full analysis set). Therefore, we ask that Labopharm check the dataset and program.

Finally, please disregard our June 19, 2006 e-mail request, as Labopharm's May 2, 2006 submission addressed our requests for information whether or not each patient studied, belonged to Safety Population, Full Analysis Population, ITT Population, and Per Protocol Population for Studies MDT3-001, -002, and -003.

We request a prompt written response in order to continue our evaluation of your NDA. If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
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E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
6/21/2006 03:10:12 PM
CSO

From: Balcer, Paul
Sent: Wednesday, June 07, 2006 3:19 PM
To: Becky Prokipcak PhD, RAC
Cc: 'rouellet@labopharm.com'
Subject: NDA 21-745 (tramadol hydrochloride extended release tablets) - CMC Information request.
Importance: High

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride extended release tablets) 100, 200 and 300 mg.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) module 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.

CMC:

1. The non-proprietary name of the drug product should be "tramadol hydrochloride extended release tablets." The NDA proposed term "controlled release" should not be used. Accordingly, revise the labels and labeling.

2. It is stated in section 3.2.P.4.4 that the specification of _____ is based on the supplier's specification. However, the certificates of analysis from _____ indicate the following additional tests performed by _____: content of povidone, content of polyvinyl acetate, residual solvents, and microbial limits. These tests are needed to ensure the quality and purity of _____ and should be included in the NDA specification for this excipient. Accordingly, provide revised specifications for this excipient. b(4)

3. Appropriate acceptance criteria (range/limit) should be established for the test of average weight in the drug product specification for stability. The specification, as presented in Table 3.2.P.5.1-2, inadequately includes "report results" for the test.

4. Provide parameters and setting for _____ that are controlled to ensure hardness and core-centering. b(4)

5. The NDA provided sampling frequency only in the Master Batch Record, but not in the section 3.2.P.3.4 Control of Critical Steps and Intermediates for Drug Product. Please add the sampling plan for in-process control and release testing in this section and submit revised section.

6. A separate content uniformity test for the Core should be established and controlled.

7. The following comments pertain to the container closure systems:

   (a) Please provide assurance of safety of all packaging components (as listed in table 3.2.P.7-2) by reference to appropriate 21CFR food additive regulations.

   (b) Provide USP <671> testing results for blister packaging systems (as shown in Table 3.2.P.7-1). For the bottles, please confirm that the inner seals were removed prior to USP <671> testing (refer to section III.G of the "Guidance for

Industry, Container Closure Systems for Packaging Human Drugs and Biologics") and provide test results in mg/day/L.

8. The following comments pertain to the matrix design for the annual stability batches (Protocol PT-0255.1):

   (a) Provide the matrix program for the proposed container closure systems (as described in Table 3.2.P.7-1). Please indicate clearly (in the table for the matrix program) what container closure systems that C_1 through C_5 represent.
   (b) It is stated in your protocol that "if more than 3 marketed container closure systems are planned within a campaign, the analysis will be done according to a matrix." Please clarify this statement and state whether all the container closure systems described in Table 3.2.P.7-1 will be used for marketed drug product.

9. The analytical method for Core Centering involved: [redacted] b(4)

   [redacted] Provide a commitment with a timeline that a more robust method would be investigated (e.g. automated on-line monitoring method) and developed.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg 22 Rm 3145
Silver Spring MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
6/7/2006 04:28:51 PM
CSO

Appears This Way
On Original

From: Balcer, Paul
Sent: Wednesday, May 03, 2006 1:47 PM
To: 'Becky Prokipcak'
Subject: NDA 21-745 (Tramadol CONTRAMID OAD) - Clarification of the second Information request (CMC).

Importance: High
Sensitivity: Confidential

Follow Up Flag: Review
Flag Status: Flagged

Dear Dr. Prokipcak,

The following clarifications are presented below:

1. To which address should the samples be submitted to? Please advise us of a contact person, if applicable.

These samples are for the reviewers to visually examine the tablets, and are not for the purpose of method validation. Please mail the samples as a desk copy to my attention.

2..According to CFR.314.50(e), samples must be submitted in sufficient quantity to permit FDA to perform three times each test. Please confirm that the following sample design is appropriate to meet the FDA request. Note: Approximately 300 tablets will be provided for each packaging format (Bottle or blister).

100 mg: Lot A (Bottles), Lot A (Blisters)

200 mg: Lot B (Bottles) Lot B (Blisters)

300 mg: Lot C (Bottles), Lot C (Blisters)

If the sample design is not appropriate, could you please confirm what your requirements would be.

For each strength, please provide the tablets in a bottle and a blister box. For the bottles, it is not necessary to send the drug product in each bottle size.
The smallest bottle size (30 tablets) for each strength is sufficient.

3. We will provide a certificate of analysis for each lot of sample submitted. We will also provide samples of the reference standard for tramadol and the impurity, with the COAs. As a complete method validation package was included in the NDA, does the FDA require any further documentation to be submitted along with the samples?

None is required at this time.

Best regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products

FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVE
BLDG 22 RM 3145
SILVER SPRING MD 20993-0002
Phone: (301) 796 1173
Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

From: Becky Prokipcak [mailto:bprokipcak@canreginc.com]
Sent: Wednesday, April 26, 2006 8:51 AM
To: Balcer, Paul
Subject: RE: NDA 21-745 Tramadol Contramid OAD - Information request (#2)
Sensitivity: Confidential

Hi Paul

As we discussed in the teleconference yesterday, we would like to receive the following clarifications to the CMC question from April 20, 2206, "Provide samples for each strength in each proposed packaging system":

1.. To which address should the samples be submitted to? Please advise us of a contact person, if applicable.

2.. According to CFR.314.50(e), samples must be submitted in sufficient quantity to permit FDA to perform three times each test. Please confirm that the following sample design is appropriate to meet the FDA request. Note: Approximately 300 tablets will be provided for each packaging format (Bottle or blister).

100 mg: Lot A (Bottles), Lot A (Blisters)

200 mg: Lot B (Bottles) Lot B (Blisters)

300 mg: Lot C (Bottles), Lot C (Blisters)

If the sample design is not appropriate, could you please confirm what your requirements would be.

3.. We will provide a certificate of analysis for each lot of sample submitted. We will also provide samples of the reference standard for tramadol and the impurity, with the COAs. As a complete method validation package was included in the NDA, does the FDA require any further documentation to be submitted along with the samples?

Many thanks for your help with this. We should be able to send the samples shortly after receiving clarification on these points.

All the best,

Becky

From: Balcer, Paul [mailto:paul.balcer@fda.hhs.gov]
Sent: Thursday, April 20, 2006 12:39 PM
To: Becky Prokipcak
Subject: NDA 21-745 Tramadol Contramid OAD - Information request (#2)
Importance: High
Sensitivity: Confidential

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) and Biostatistics sections 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.

CMC:

a.. Provide samples for each strength in each proposed packaging system.

Biostatistics:

a.. Provide information, in SAS transport file, whether or not each patient studied, belongs to Safety Population, Full Analysis Population, ITT Population, and Per Protocol Population for Studies MDT3-001, -002, and -003, and also provide the derived efficacy SAS data sets for each study.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer

Regulatory Health Project Manager

Division of Anesthesia, Analgesia

and Rheumatology Products

FOOD AND DRUG ADMINISTRATION

10903 NEW HAMPSHIRE AVE

BLDG 22 RM 3145

SILVER SPRING MD 20993-0002

Phone: (301) 796 1173

Fax: (301) 796 9713

E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
5/3/2006 01:58:42 PM
CSO

BlankFrom: Balcer, Paul
Sent: Thursday, April 20, 2006 12:39 PM
To: 'Becky Prokipcak'
Subject: NDA 21-745 Tramadol Contramid OAD - Information request (#2)

Importance: High
Sensitivity: Confidential

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) and Biostatistics sections 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.

CMC:

- Provide samples for each strength in each proposed packaging system.

Biostatistics:

- Provide information, in SAS transport file, whether or not each patient studied, belongs to Safety Population, Full Analysis Population, ITT Population, and Per Protocol Population for Studies MDT3-001, -002, and -003, and also provide the derived efficacy SAS data sets for each study.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVE
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E-mail: paul.balcer@fda.hhs.gov

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/s/

Paul Balcer
4/20/2006 05:28:25 PM
CSO

MEMORANDUM

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

DATE: April 11, 2006

TO: Robert Rappaport, M.D., Director
Division of Analgesics, Anesthetics, & Rheumatology Products, HFD 170

FROM: Claudia B. Karwoski, Pharm.D.,
Scientific Coordinator for Risk Management Programs
Office of Drug Safety, HFD-400

DRUG: Tramadol Contramid OAD (tramadol hydrochloride controlled release)

NDA: 21-745

SPONSOR: Labopharm Canada, Inc.

SUBJECT: ODS Review of Proposed Risk Management Plan (RMP) dated November 25, 2005

PID #: D060174

The sponsor's proposed Risk Management Plan for Tramadol Contramid OAD (tramadol hydrochloride controlled release); NDA 21-745, does not appear to differ substantially from typical new product labeling. Although the Sponsor does not include post-marketing surveillance as part of the Risk Management Plan for Tramadol Contramid OAD, this product, if approved, will be subject to routine post-marketing safety surveillance as required by 21CFR314.80.

Tramadol Contramid OAD is a once-daily formulation of tramadol comprising both immediate-release and controlled-release components. The proposed indication is the management of moderate to moderately severe pain. Tramadol, a centrally acting analgesic, is an approved product already on the U.S. market.[1]

---

[1] Tramadol is currently available as a single-ingredient tablet (both immediate-release and extended-release), and in a tablet in combination with acetaminophen.

The Sponsor's submission does not identify any unique safety issues with this product for which a Risk Minimization Action Plan (RiskMAP) to minimize risk normally would be associated. We also note that tramadol products, marketed for approximately 11 years, to date have not required risk management tools beyond standard product labeling and routine post-marketing safety surveillance. If the sponsor or the Review Division identifies a safety concern and determines that a RiskMAP is warranted, please refer to the most recent publicly available information on CDER's views on RiskMAPs, *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, which can be located electronically at http://www.fda.gov/cder/guidance/6358fnl.htm.

Should the review division want ODS to review a future RiskMAP submission please send a consult to ODS and notify the ODS-IO Project Manager, Mary Dempsey, at 301-796-0147.

Claudia B. Karwoski, PharmD

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/s/

Mary Dempsey
4/11/2006 03:25:30 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
4/12/2006 07:21:05 AM
DRUG SAFETY OFFICE REVIEWER

CDocuments and SettingsbalcerpDesktopNDA21745Information request031506.txt
From: Balcer, Paul
Sent: Wednesday, March 15, 2006 3:07 PM
To: 'Becky Prokipcak, PhD'
Subject: NDA 21-745 Tramadol Contramid OAD - Information request.

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Prokipcak:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet. Additionally, please refer to your February 20, 2006 e-mail response to our February 10, 2006 filing letter.

We are reviewing the Biophamaceutical and Chemistry, Manufacturing and Controls (CMC) sections 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.

CMC:

1. Stability data should be submitted in SAS transport format. This is a file format used for presenting data such as clinical trial data, stability data, etc. If the files are unavailable in this format, submit the stability data in MS Excel spreadsheet.

2. Submit statistical analysis of all stability-indicating attributes; this should include regression fits and 95% confidence intervals around them.

Biopharmaceutics:

* Provide raw PK data in SAS format for studies MDT 1-006, MDT 1-009 and MDT 1-011 and any ongoing studies.

General

1. Provide a color version of the packaging.

2. Provide a legible copy of the November 3, 2005 initial waiver letter from Ortho-McNeil, Inc. to Dr. Rappaport.

If you have any questions, please contact me.

Regards,

Paul Z. Balcer
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVE
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Fax: (301) 796 9713
E-mail: paul.balcer@fda.hhs.gov

CDocuments and SettingsbalcerpDesktopNDA21745Information request031506.txt

---

From: Becky Prokipcak, PhD [mailto:bprokipcak@canreginc.com]
Sent: Monday, February 20, 2006 4:53 PM
To: Balcer, Paul
Subject: NDA 21-745 CMC Response

Hi Paul

In the NDA 21-745 filing communication of Feb. 10, there was a CMC request as follows: "Provide the statistical analysis program of the stability test data described in the NDA in SAS format."

In response to this request, I have the following reply from the Labopharm CMC team:

"We do not have our stability data available in SAS format. We understand that our NDA contains a great deal of stability data, including a significant amount at room temperature. We would propose a teleconference to discuss what could be provided by Labopharm to ease the review of the stability data by the CMC reviewer."

Please let me know if you are in agreement with our proposal, and if so, what days and times might work for organizing a teleconference.

Thanks and all the best,

Becky

Becky Prokipcak, PhD, RAC

Sr. Director, Regulatory Affairs

CanReg Inc.

1-866-722-6734

www.canreginc.com

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/s/

Paul Balcer
3/15/2006 03:22:36 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

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:

Please refer to your November 25, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on February 10, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

CLINICAL PHARMACOLOGY

Please refer to our January 27, 2006 teleconference where we agreed that you would address the following issues by June 30, 2006:

1. The product used in the pivotal clinical trials and the product proposed to be commercially marketed are manufactured in two different manufacturing sites. There is inadequate data linking the products manufactured at these two sites.

2. Food effect was determined on the 200-mg strength. However, [redacted] the food effect for the 300-mg strength may be different. As such, potential dose dumping of the 300-mg strength due to food effect has not been completely ruled out.

b(4)

Submission by the agreed upon date will facilitate timely review of the NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

CMC

1. Provide the statistical analysis program of the stability test data described in the NDA in SAS format.

2. Provide the Chemistry, Manufacturing and Control information for the control-release agent, Contramid. This should include chemical synthesis/manufacturing information, regents, solvents, flow chart, structural elucidation and characterization, test methods and specifications, stability, etc.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Paul Z. Balcer, Regulatory 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
2/10/2006 05:06:50 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

NDA ACKNOWLEDGMENT

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 have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Tramadol Contramid® OAD (tramadol hydrochloride) 100, 200 and 300 mg controlled release tablet
Review Priority Classification:	Standard (S)
Date of Application:	November 25, 2005
Date of Receipt:	November 28, 2005
Our Reference Number:	NDA 21-745

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 27, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 28, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a pediatric deferral and your request for a partial waiver for pediatric studies in infants and children (0 to 12 years). Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Paul Z. Balcer
Regulatory Healthcare 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/

Paul Balcer
12/8/2005 04:38:28 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Labopharm Canada
480 Armand-Frappier Blvd.
Laval, Québec, Canada H7V 4B4

2. TELEPHONE NUMBER *(Include Area Code)*
(888) 686-1017

3. PRODUCT NAME
Tramadol Contramid OAD

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-745

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☒ YES ☐ NO
(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Becky Richard	Sr. Director, Regulatory Affairs	11/25/2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	see attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
James Howard-Tripp	President and CEO
FIRM / ORGANIZATION	
Labopharm Inc.	
SIGNATURE	**DATE**
	24 Oct, 2005.

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (2/03)