CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-964

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-964 SUPPL # NA HFD # 180

Trade Name Relistor

Generic Name Methylnaltrexone bromide

Applicant Name Progenics Pharmaceuticals, Inc.

Approval Date, If Known expected April 24, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

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

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

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form:
Title:
Date:

Name of Office/Division Director signing form:
Title:

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

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

/s/

Joyce Korvick
4/23/2008 02:28:19 PM

Debarment Certification Statement

In connection with this application (NDA #21,964), Progenics Pharmaceuticals, Inc., by its undersigned officer, 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.

Progenics Pharmaceuticals, Inc.

Signed: _____ Title: SENIOR VICE PRESIDENT

Print: MARK R. BAKER Date: 30/JAN/2007

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA# : 21-964 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: 3/30/07 **PDUFA Goal Date:** 1/30/08 – initial, extended to 4/30/08

HFD 180 **Trade and generic names/dosage form:** Relistor (methylnaltrexone) SC Injection

Applicant: Progenics Pharmaceuticals **Therapeutic Class:** cathartics and laxatives

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

X **Yes. Please proceed to the next question.**

☐ **No. PREA does not apply. Skip to signature block.**

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

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

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

Number of indications for this application(s): 1

Indication #1: Proposed: Treatment of opioid-induced constipation in patients receiving palliative care

Is this an orphan indication?

☐ **Yes. PREA does not apply. Skip to signature block.**

X **No. Please proceed to the next question.**

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

☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

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

Min____ kg____ mo.____ yr. birth Tanner Stage____
Max____ kg____ mo.____ yr. 5 Tanner Stage____
Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

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

Min ____ kg____ mo.____ yr. 6 Tanner Stage____
Max____ kg____ mo.____ yr. 17 Tanner Stage____

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

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

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Matthew Scherer
3/19/2008 11:10:09 AM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]			
BLA # NDA # 21-964	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Relistor Established Name: Methylnaltrexone bromide Dosage Form: Subcutaneous Injection		Applicant: Progenics Pharmaceuticals, Inc.	
RPM: Matthew Scherer		Division: HFD-180	Phone # 301-796-2307

NDAs: NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date: ❖ Action Goal Date (if different):	4-30-08 4-24-08
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

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

Version: 3/13/08

❖ Application Characteristics	
Review priority: X Standard ☐ Priority Chemical classification (new NDAs only): Type 1 (NME) NDAs, BLAs and Supplements: ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies NDAs and NDA Supplements: ☐ OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	3-19-08
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None X HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs only: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	Included 4-23-08
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:

❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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

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

(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	Included 4-23-08
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	Included 4-23-08
❖ Documentation of consent/non-consent by officers/employees	Included 4-23-08
Decisional Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	Included 4-24-08
❖ Division Director Summary Review *(indicate date for each review)*	Included 4-24-08
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	NA
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 4-24-08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	4-24-08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	3-30-07
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	4-24-08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	3-30-07

• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
❖ Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	NA
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	Included, received 4-16-08
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	X RPM 3-17-08 X DMEDP 4-11-08, 3-28-08, 8-2-07 X DRISK 4-4-08 ☐ DDMAC ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	X Included 6-1-07
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included 4-23-08
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	NA
❖ Pediatric Page *(a new Pediatric Page for each review cycle)*	X Included 3-19-08
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	X None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	Included, received 3-7-08 (Peds plan)
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	Included, 2-29-08
• Regulatory Briefing	X No mtg

• Pre-NDA/BLA meeting *(indicate date)*	8-15-05, 11-1-04 ☐ No mtg
• EOP2 meeting *(indicate date)*	7-10-03 ☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meetings	X No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	2-5-08 ☐ None
❖ PAL/BUD Review(s) *(indicate date for each review)*	6-5-08 ☐ None
❖ CMC/product quality review(s) *(indicate date for each review)*	4-23-08, 2-4-08, 6-5-07 ☐ None
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	X None
❖ BLAs: Product subject to lot release (APs only)	NA
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 2-4-08 CMC review p.85
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	11-30-07
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 7-5-07 X Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	4-24-08 ☐ None
❖ Supervisory Review(s) *(indicate date for each review)*	X None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11-29-07 ☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	NA
❖ Nonclinical inspection review summary (DSI)	X None requested

Clinical Information	
❖ Clinical Team Leader Review(s) *(indicate date for each review)*	Included 3-28-08
❖ Clinical review(s) *(indicate date for each review)*	3-6-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	See 3-6-08 Clinical review p.23
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	2-25-08, 2-4-08, 8-28-07
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	X Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See 3-6-08 Clinical review p.97
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	
• Clinical Studies	12-6-07
• Bioequivalence Studies	NA
• Clinical Pharmacology Studies	NA
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	X None
❖ Statistical Team Leader Review(s) *(indicate date for each review)*	X None
❖ Statistical Review(s) *(indicate date for each review)*	3-7-08, 6-13-07 ☐ None
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	3-11-08, 12-14-07 ☐ None

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.

(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.

(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

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

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

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

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

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

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

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

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

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

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

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

From: Scherer, Matthew
Sent: Monday, April 14, 2008 10:07 AM
To: 'AnnMarie Assumma'
Subject: Relistor labeling comments

Dear Ms. Assumma,

We have reviewed the labeling components sent via email on April 7, 2008. We request the following changes:

For all Labels and Labeling

1. In the proprietary name, present the letter "O" without the graphic.
2. Relocate the strength to appear directly beneath the established name.
3. Relocate the "Sterile Single Use Vial" and "Discard after use" statements so they appear directly beneath the route of administration statement ("For Subcutaneous Injection Only").

For Trade and Sample Tray Lidding

1. Increase the size of the "Protect vial from light" statement.
2. In the tray contents section, add the size of the syringe.

For Trade and Sample Carton Labeling

1. Increase the size of the "Protect vial from light" statement.
2. In the tray contents section, add the size of the syringe.
3. Remove the word " — from the content statement on the principal display panel. Change the statement to read "Each carton contains 7 trays. Each tray contains one sterile single use vial. Discard after use."

Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

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/s/

Matthew Scherer
4/15/2008 02:50:18 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	February 29, 2008
TIME:	10:00 AM
LOCATION:	White Oak, Room 5270
APPLICATION:	21-964
DRUG NAME:	Relistor (methylnaltrexone bromide) S.C. Injection
TYPE OF MEETING:	Pre-Approval Safety Conference
MEETING CHAIR:	Ruyi He, Medical Team Leader
MEETING RECORDER:	Matthew Scherer, Regulatory Project Manager

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III
Donna Griebel, MD, Director, Division of Gastroenterology Products
Joyce Korvick, MD, MPH, Deputy Director, Division of Gastroenterology Products
Ruyi He, MD, Medical Team Leader, Division of Gastroenterology Products
Ron Orleans, MD, Medical Reviewer, Office of Drug Evaluation III
Tamara Johnson, MD, Medical Reviewer, Division of Gastroenterology Products
Sushanta Chakder, PhD, Supervisory Pharmacologist, Division of Gastroenterology Products
Tamal Chakraborti, PhD, Pharmacologist, Division of Gastroenterology Products
Kate Dwyer, PhD, Statistical Reviewer, Division of Biometrics
CAPT E. Dennis Bashaw, PharmD, Director, Division of Clinical Pharmacology III
Insook Kim, PhD, Clinical Pharmacology Reviewer, Division of Pharmaceutical Evaluation III
Claudia Karwoski, PharmD, Acting Director, Division of Risk Management, Office of Surveillance and Epidemiology
Allen Brinker, MD, Medical Officer, Division of Epidemiology, Office of Surveillance and Epidemiology
Lanh Green, PharmD, MPH, Safety Evaluator Team Leader, Division of Adverse Event Analysis 1, Office of Surveillance and Epidemiology
Ann Corken Mackey, RPh, MPH, Safety Evaluator, Division of Adverse Event Analysis 1, Office of Surveillance and Epidemiology
Matthew Scherer, Regulatory Project Manager, Division of Gastroenterology Products

BACKGROUND:

New Drug Application (NDA) 21-964 was submitted March 30, 2007 by Progenics Pharmaceuticals, Inc. This NDA seeks to market Relistor (methylnaltrexone bromide) Subcutaneous Injection for the treatment of opioid-induced [redacted] in advanced illness patients receiving palliative care. Methylnaltrexone bromide is a new molecular entity (NME). As such, a pre-approval safety conference with the appropriate representatives of the Office of Surveillance and Epidemiology (OSE) is required.

MEETING OBJECTIVES:

- To satisfy the pre-approval safety conference requirement
- To determine what means are necessary to minimize the risk associated with the use of Relistor, should it be approved

DISCUSSION POINTS:

- It was noted that methylnaltrexone, like alvimopan, is a mu opioid receptor antagonist. A detailed comparison of the pharmacological properties of methylnaltrexone and alvimopan was presented demonstrating that, despite being members of the same pharmacological class, the drugs have some vastly different properties (e.g., receptor affinity, inhibition, etc). There is insufficient data to demonstrate a class effect.
- It was noted that, because Relistor is administered through subcutaneous injection, an epidemiological assessment will be very difficult. It was further noted neither MedWatch nor claims data are likely to detect a cardiovascular signal resulting from the use of Relistor.
- It was noted that methylnaltrexone may be improperly used in the setting of fecal impaction. The labeling group was asked to consider text within approved labeling that would guide clinicians into consideration of the primary indication and further measures to take if methylnaltrexone did not produce the desired effect.
- Post-approval monitoring will focus on the adverse events most commonly observed in Relistor's supporting clinical trials (abdominal pain, nausea and dizziness) as well as cardiovascular events (including QT prolongation), hepatotoxicity and dehydration.
- It was agreed that the safety profile of methylnaltrexone did not warrant a risk management plan (RiskMAP).
- It was agreed that, other than pediatric studies, no additional studies would be requested as post-marketing commitments/requirements (PMCs/PMRs).

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/s/

Matthew Scherer
4/11/2008 05:02:22 PM

From: Scherer, Matthew
Sent: Wednesday, March 19, 2008 1:25 PM
To: 'AnnMarie Assumma'
Subject: NDA 21-964 Labeling Review of SPL-DLDE

Attachments: methylnaltrexone_bromide_spl_dldes_rev (2).pdf

AnnMarie,

Please revise the information in Drug Listing Data Elements in Structured Product Labeling as shown in the attached file.

methylnaltrexone_bromide_spl_d...

Regards,

Matthew C. Scherer
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9905

__2__ Page(s) Withheld

__X__ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- __1__

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/s/

Matthew Scherer
3/19/2008 01:34:03 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

ADVICE LETTER

Progenics Pharmaceuticals, Inc.
Attention: Ann Marie Assumma
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Assumma:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relistor (methylnaltrexone) Subcutaneous Injection.

We also refer to your submission dated September 28, 2007 which included a revised package insert in SPL format.

The following issues/deficiencies have been identified in your proposed labeling. Please address these issues as soon as possible.

Highlights Section:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

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

  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

  Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Use command language whenever possible (i.e., use "Advise" rather than "Patients should be advised"). [See **WARNINGS AND PRECAUTIONS**]

- Add adverse reaction inclusion criterion (e.g., incidence rate greater than X%). [21 CFR 201.57(a)(11)]

- A revision date must appear at the end of the highlights. However, for a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. [21 CFR 201.57(a)(3)]

Full Prescribing Information: Contents:

- If the Highlights and Table of Contents do not fit on one page, insert Table of Contents on page 2.

- Only section and subsection headings should appear in Contents. Delete subsection headings [illegible] from Table of Contents heading **14 CLINICAL STUDIES**.

- Delete [illegible] heading and corresponding section in the Full Prescribing Information (FPI).

Full Prescribing Information (FPI):

- **12.3 Pharmacokinetics** is a required sub-heading. Please re-order sub-headings 12.3 and 12.4. [21 CFR 201.56(d)(1)]

- Please add subheading **13.2 Animal Toxicology and/or Pharmacology**. [21 CFR 201.56(d)(1)]

- Avoid using internal company study titles (e.g. Study 301, 301EXT).

- Patient Counseling Information must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)] Please use command language and provide subheadings and numbering for each item in this section. **[See 17 for PATIENT COUNSELING INFORMATION].**

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
3/19/2008 12:59:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: ODS **Cherye Milburn, Regulatory Project Manager, OSE**	**Matthew Scherer, Regulatory Project Manager, Division of Gastroenterology Products**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 4, 2008	NA	21-964	Patient Instruction on PI	9-28-07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Relistor	standard	Mu opioid receptor antagonist Cathartic/laxative	March 11, 2008

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Hello, as discussed at the pre-approval safety conference, please review the patient instructions beginning in section 17—of the most recent PI label submission (9-28-08 in the EDR) for NDA 21-964 ——— – methylnaltrexone bromide).

We have labeling meetings scheduled for 3/6, 3/11, 3/20, 3/31. The PDUFA goal date is 4/30/08 but we intend to take action in the first week of April 2008.

Please contact myself, Ruyi He (Team Leader), Ron Orleans (Med Officer) if you have any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Matthew Scherer	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Matthew Scherer
3/4/2008 10:58:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

Progenics Pharmaceuticals, Inc.
Attention: Ann Marie Assumma
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Assumma:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (methylnaltrexone) Subcutaneous Injection.

On December 7, 2007, we received your submission of a QT study report, dated December 7, 2007. This submission has been classified as a major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2008.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
1/8/2008 01:39:38 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 12/3/2007

TO: Brian Strongin, Regulatory Project Manager
Ronald Orleans, M.D., Clinical Reviewer
Division of Gastrointestinal Products, HFD-180

FROM: Khairy Malek, M.D., GCP1 Reviewer

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

SUBJECT: Evaluation of Clinical Inspections

NDA: # 21-964

APPLICANT: Progenics Pharmaceuticals, Inc.

DRUG: Methylnaltrexone Injection

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Relief of symptomatic constipation due to —— opioid therapy
In patients with advanced medical illness.

CONSULTATION REQUEST DATE: May 31, 2007

DIVISION ACTION GOAL DATE: January 30, 2008

PDUFA DATE: January 30, 2008

I. BACKGROUND:

Methylnaltrexone is a derivative of the opioid antagonist naltrexone. The methyl derivative does not cross the blood brain barrier in humans and so has the potential to block the opioid side effects (constipation), while sparing the centrally mediated analgesic effect.

Two protocols were used in support of this NDA: MNTX 301 and MNTX 302.

MNTX 301: A Double-Blind Placebo Controlled Study of Methylnaltrexone (MNTX) for the Relief of Symptomatic Constipation Due to Chronic Opioid Therapy in Patients with Advanced Medical Illness.

MNTX 302: A Double Blind Phase 3, Two-Week, Placebo Controlled Study of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Opioid Therapy in Advanced Medical Illness.

NDA # 21-964, Methylnaltrexone:

Summary Report of U.S. Inspections:

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol	Inspection Date	EIR Received Date	Final Classification
		MNTX 301	8/23-9/6/07	9/27/07	VAI
		MNTX 301	10/8-10/12/07	11/16/07	VAI
		MNTX 302	10/1-10/5/07	11/7/07	VAI
		MNTX 302	9/10-9/29	10/01/07	VAI

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

A. Protocol # MNTX 301

1.] ——— · Site # 13:

a. At this site, 27 subjects were randomized and completed the study. The field investigator reviewed the records of all subjects at the study site.

b. There were no limitations of the inspection.

c General observations/commentary:

1. Protocol Violations:
   - Subjects # 13-06 and 07, received the first open-label dose after less than 24 hours after the double- blind dose as the protocol requires.
   - The protocol requires a 30 day follow-up assessment for the study subjects. Three subjects (13-01, 07, and 13) had their assessments after longer intervals.

2. Failure to promptly report adverse experiences to the sponsor and the IRB.

   - Subject # 13-14 experienced severe delirium dated 6/21/04. This was reported to the IRB on 7/26/04.
   - Subject # 13-23 was hospitalized on ———, for severe hematuria and died on ——— The sponsor was notified on 1/28/05 and the IRB on 2/17/05.
   - Subject # 13-02 suffered a respiratory tract infection on 10/03/03 This was reported to the IRB on 1/17/05.
   - Subject # 13-15 passed away on ——— The sponsor and the IRB were informed on 10/20/04.

These violations would not affect the validity of the data and the data from this site can be used in support of the NDA.

2. ———

a. At this site, 26 subjects were screened, 24 completed the double-blind phase, 22 enrolled in the open-label phase and 13 completed the study. The field investigator reviewed all the subjects' records.

b. There were no limitations to the inspection.

c. Observations/Commentary:

1. Protocol Violations:

- Subject # 7-19 did not have assessments of constipation distress, pain evaluation, or opioid withdrawal scale assessment before the day 1 dose of the open-label phase.
- Subject # 7-22 did not have these assessments for the 4-hour post Day 1dose.
- Subject # 16 did not have a temperature taken, 4 hours after dosing.

2. Inaccurate Records:

- Subject # 7-14 had a pain score of 0 in the worksheet for the Pain/Opioid Withdrawal assessment while it was entered in the CRF as a score of 3.

3. Inaccurate Drug Accountability Record.

The drug accountability record for the open-label study was missing 75 vials unaccounted for.

These violations would not affect the validity of the data and the data from this site can be used in support of the NDA.

B. Protocol MNTX 302:

3. _____

a) At this site, 9 subjects were enrolled and 8 completed the 2-week study (one dropped out). The field investigator reviewed the records of all subjects in the study.

b) There were no limitations to the study.

c) Observations/Commentary:

1. Protocol Violations:

- Subjects # 17-01, 03, 05, 06, 09, 10, 12, and 21 completed the double-blind study before their laboratory reports were signed by the CI.

- Subjects # 17-01, 03, 12, 15, and 21 did not have some of the assessments (physical, vital signs, hematology, serum chemistry) required by the protocol, before the administration of Day 7 dose.

These violations would not affect the validity of the data and the data from this site can be used in support of the NDA.

4. _____

a) At this site, 18 were randomized, and 11 completed the study. The field investigator reviewed all the subjects' records.

b) There were no limitations to the inspection.

c) Observations/Commentary:

1. Protocol Violations:
   - Subject # 24-14 dose of the study drug was doubled although the subject had 4 bowel movements by day 8, not associated with rescue medications.
   - Subjects # 24-01, 04, 05, and 21 used rescue laxatives within less than 4 hours of the drug dose.

2. Inaccurate Records:

   There was no documentation to verify that the test article dispensed to study subjects or their caregivers was stored at 2-8 degrees Celsius as the protocol requires.

These violations would not affect the validity of the data and the data from this site can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The violations listed above, some of them due to the nature of the study being studied in terminally ill patients, would not affect the validity and acceptability of the data in support of this NDA.

Khairy W. Malek, M.D.
Reviewer
GCPB Reviewer Name
Title

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

Constance Lewin
12/6/2007 05:18:16 PM
MEDICAL OFFICER
Entered into DFS by C. Lewin on behalf of
Dr. Khairy Malek in his absence.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relistor (methylnaltrexone) Injection.

We also refer to your submission dated November 8, 2007.

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

1. [redacted]

2. The data provided in the November 8, 2007, amendment are too limited to conclude that [redacted] is not a degradant and does not increase [redacted] Please commit to the following limited testing to demonstrate that a routine test is not necessary:
   - Test the content of [redacted] at the remaining stability time points for the three registration batches, i.e. H10205, H10206, and H10207.
   - At the end of the proposed 24-month expiry period, spike the three registration batches with [redacted] and determine the recovery of [redacted]
   - Provide the results in the annual report.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
11/14/2007 02:39:44 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relistor (methylnaltrexone) Injection.

We also refer to your Chemistry Information Amendment dated October 17, 2007.

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

Per your 10/17/2007 Chemistry Information Amendment, comment #8b, the Agency would like to clarify the use of the dosage form modifier:

The dosage form modifier does not have to be included in the Drug Listing Data Elements in Structural Product Labeling. It should be included in the PATIENT LABELING section as indicated in the 8/29/2007 information request letter. Please incorporate this comment, and submit your revised labeling.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Marie Kowblansky
10/23/2007 03:29:03 PM
Marie Kowblansky, Acting Branch Chief for Moo-Jhong Rhee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relistor (methylnaltrexone) Injection.

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

1. Please provide data for product relevant extractable/leachable study for [redacted] stopper, [redacted]
2. Please clarify where the microbiological tests for the drug substance will be conducted. The method was listed as " [redacted] in the drug substance specification. However, the test results summarized in Table S.4.4.6 were not listed in the Mallinckrodt certificates of analysis (COAs) for lots H10205, H10206, and H10207.
3. Please provide mock-up container and carton labels bearing the chosen tradename. These labels should be presented in the sizes and colors proposed for marketing.
4. Please provide samples of the drug product in the proposed container closure system.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
10/5/2007 01:42:51 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Relistor (methylnaltrexone bromide) Injection.

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

> Please add a test and an acceptance criterion for _____ in the drug product release and stability specifications.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
9/11/2007 03:44:56 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone Injection.

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

1. Please lower the acceptance criterion for [redacted] to NMT [redacted] ppm in the drug substance specification as committed previously.

2. In the evaluation of the criticality of [redacted] during the manufacturing of the drug product (Wyeth Report RPT-66218), the duration of the stability study (at room temperature and at [redacted]. Please perform one of the following:
   a. Provide additional supporting data (e.g., 6 months accelerated stability data or long term stability data up to the proposed expiration date for the drug product manufactured without [redacted] to justify that the [redacted]

   or

   b. [redacted]

3. Please describe how the relative response factors for the specified impurities or degradants were determined for HPLC methods Progenics SOP 250-P- 004 (for drug substance) and Wyeth L28228-147 (for drug product). The values are quite different even though these two methods are very similar. See the table below:

Impurities	Progenics SOP 250-P-004	Wyeth L28228-147
[redacted]	[redacted]	[redacted]

*Assigned to be [redacted]

4. Please provide purity data for the reference standards of [redacted] to support their relative response factors [redacted] respectively in Wyeth HPLC method L28228-147). The response factors for [redacted] product [redacted] that of the drug substance. The relative response factor for [redacted] in Progenics HPLC method SOP 250-P-004, which is very similar to method L28228-147, was assigned to be [redacted]

5. Provide the source and lot number for the reference standards of [redacted] product and [redacted] The relative response factors for these two related substances were determined in HPLC methods, Progenics SOP 250-P-004 (for drug substance) and/or Wyeth L28228-147 (for drug product).

6. Provide the relative retention time and relative response factor for [redacted] product in Progenics Method 250-P-004 for assay and related substance.

7. Please lower the acceptance criterion for total degradants in the drug product specification to NMT [redacted], unless justified. The proposed acceptance criterion of NMT [redacted] is too high compared to the data from the clinical batches, manufacturing capability, and the demonstrated six-month stability data at 40°C for the primary stability batches.

8. Revise the following labeling information:
   a. Include all excipients in the Drug Listing Data Elements in Structured Product Labeling
   b. Revise the establish name to include "injection" inside the parenthesis following methylnaltrexone bromide as shown below in the PATIENT LABELING section and Drug Listing Data Elements in Structured Product Labeling.

      BRANDNAME Injection
      (methylnaltrexone bromide injection)

Please be reminded that the information should be submitted no later than three months prior to the PDUFA date.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/29/2007 12:49:11 PM
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alex Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone Injection.

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

1. While you have submitted a description of the analytical method and individual study validation data, the submitted data does not directly address the issue of naltrexone. Given that studies in animals have shown the potential for de-methylation to occur, please provide definitive evidence of the analytical method's ability to detect the presence of naltrexone and its primary metabolite 6beta-naltrexol in either a qualitative or quantitative way in the human studies.

2. The data set as submitted is not readily usable for pharmacokinetic analysis. Please provide a separate SAS Transport file for each of the pharmacokinetic/clinical pharmacology trials in which the data is arranged with subject number down the first column and concentration time data across the remaining columns. For example:

Subject #	Time 0	1	2	3	etc
103.001	0.0	0.2	1.2	5.7	...
103.002	0.0	0.2	1.1	5.5	...

   For studies in which subjects were crossed over to other treatment legs, the data should be separated into a separate file identified by treatment.

3. With regards to the data analysis itself, some calculations appear to be errant. For example, in MNTX-1107, examination of the data fitting for half-life suggests that inconsistent rules were used in the treatment of data. Specifically for subject 01-808 it appears that the last timepoint is spurious for an unexplained reason. Allowing the computer to estimate half-life based on 19 data points and then rejecting the subject from the analysis is not indicative of a

careful analysis of the data. The same can be said of subject 03-807 where the computer was allowed to use 18 data points to estimate the half-life. A complete reanalysis is unnecessary, however, please review your data integrity plan as well as the submitted data analysis and make any appropriate updates to the analysis to demonstrate adequate data quality assurance.

4. As part of the resolution of the issue identified above, please provide a re-calculation of half-life with a truncation of the data at 48 hours. As the majority of the spurious data points occur post-48 hours, this should provide better estimates.

5. There are some errors in your reports in which figures are mislabeled or do not match the data in the corresponding tables. For example:

   In study MNTX-1107, Figure 16.2.8-2, the plasma concentration profiles for subjects 01-801 and 01-802 are labeled as log-linear but are presented as standard linear plots. Please check data and provide corrected plots.

   In section 16.2.6.1, the summary table for terminal half-life contains values that are markedly different from the data presented elsewhere. Considering that this is a summary table, these discrepancies are concerning and need to be clarified or justified. See the table entitled "Terminal Half-Life Data Summary Figures and Tables" and compare these half-life estimates with the estimates it purports to summarize on the preceding figures.

6. Please provide figures of the individual cumulative urinary excretion data vs. times or direct us to such a plot in the NDA.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
8/29/2007 12:31:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

INFORMATION REQUEST LETTER

Progenics Pharmaceuticals, Inc.
Attention: Alexander W. Rochefort
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone bromide injection.

We are reviewing the Statistical section of your submission and have the following information requests regarding your studies entitled "A Double-Blind, Placebo-Controlled Study (with an Extension Study) of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Chronic Opioid Therapy in Patients with Advanced Medical Illness" (MNTX 301) and "A Double-Blind, Phase 3, Two-Week, Placebo Controlled Study of Methylnaltrexone (MNTX) for the Relief of Constipation Due to Opioid Therapy in Advanced Medical Illness" (MNTX 302). We request a prompt written response in order to facilitate our evaluation of your NDA.

1. Please submit a detailed definition of rescue laxation.

2. Please provide detailed formulas for computation of the following derived variables. Specify raw variables and provide data documentation.
   - RFRESP4H
   - RFRSP24H
   - RFBM1ST

3. Please provide a data file with the following information:
   - Subject I.D.
   - Treatment Group
   - Treatment Period (Epoch=DB)
   - Time of First Rescue Laxation (Post Treatment in hours)
   - Time to First Laxation (Post Treatment in hours)
   - Study Day (302 only)

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at 301-796-2307.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, M.S.N., R.N.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
6/27/2007 08:26:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-964

Progenics Pharmaceuticals, Inc.
Attention: Alexander W. Rochefort
Senior Director, Regulatory Affairs
Old Saw Mill River Road
Tarrytown, New York 10591

Dear Mr. Rochefort:

Please refer to your March 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylnaltrexone Injection.

We also refer to your submission dated May 31, 2007.

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) of the Act on May 29, 2007 in accordance with 21 CFR 314.101(a).

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

Statistical

We have been unable to locate information about the interim analysis plan for Study MNTX 301. We have been unable to locate information about the interim analysis plan and the interim analysis report for Study MNTX 302.

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:

Statistical

1. For Study MNTX 301, please provide either:

    - The location within the application of the pre-specified Interim Analysis Plan for sample size re-estimation, or
    - Submit the plan with the sign-off sheet with signatures and dates

2. For Study MNTX 302, please provide both the pre-specified Interim Analysis Plan with the sign off sheet with signatures and dates and the Interim Analysis Report.

3. Provide a data file with the following information for each Phase III Study:
   - Subject I.D.
   - Treatment Group
   - Flag to identify which subjects were used in the interim analysis

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 me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
6/12/2007 11:33:30 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
Corinne Moody, HFD-009 RKWL #2, Room 1205	Brian Strongin, HFD-180 White Oak #22, Room 5116

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 9, 2007		21-964	New NDA submission	3/30/07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Methylnaltrexone Injection	Standard	1 S	11/30/07

NAME OF FIRM: Progenics Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Methylnaltrexone is a peripherally acting mu-receptor antagonist indicated for the treatment of opioid-induced constipation in patients receiving palliative care. Please review and evaluate for abuse potential. This is an eCTD NDA and the entire submission is available in the EDR under the NDA number. The Medical Team Leader assigned to this NDA is Fathia Gibril (6-0898). The Medical Officer assigned to this NDA is Ron Orleans (6-0964). Thanks. Brian Strongin 6-1008.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☐ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Brian Strongin
6/8/2007 09:27:35 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: June 6, 2007

To: Alex Rochefort	**From:** Brian Strongin
Company: Progenics Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number:	**Fax number** (301) 796-9905
Phone number:	**Phone number:** (301) 796-1008

Subject: NDA 21-964: Pharm-Tox Information Request

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

Please submit the following information to NDA 21-964 ASAP:

1. A list of all pre-clinical studies previously submitted under IND 64,583, including the serial numbers and submission dates.

2. A list of all pre-clinical studies previously submitted under IND ___ including the serial numbers and submission dates.

3. A list of all new pre-clinical studies that were not previously submitted under either of the above INDs and are submitted in the NDA.

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/s/

Brian Strongin
6/7/2007 01:53:13 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-964 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: N/A
Established Name: Methylnaltrexone Bromide Injection
Strengths: 12 mg/0.6mL

Applicant: Progenics Pharmaceuticals, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: March 30, 2007
Date of Receipt: March 30, 2007
Date clock started after UN: N/A
Date of Filing Meeting: May 29, 2007
Filing Date: May 29, 2007
Action Goal Date (optional): January 30, 2008 User Fee Goal Date: January 30, 2008

Indication(s) requested: Treatment of opioid-induced constipation in patients receiving palliative care

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.) 1
Other (orphan, OTC, etc.) N/A

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

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

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:

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: All forms are in paper and signed in volume 1.1.

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 5 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)? **N/A** 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. **Yes**

- List referenced IND numbers: IND —— IND 64,583; IND ——

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections. **(Tradename has not been approved yet and is not in COMIS.)**

- End-of-Phase 2 Meeting(s)? Date(s) EOP2 Mtg - July 10, 2003 NO ☐
  QT T-Con – April 4, 2004
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Pre-NDA Mtg CMC – November 1, 2004
  Pre-NDA Mtg – August 15, 2005
  Biopharm T-Con – August 31, 2005
  Pre-NDA CMC T-Con – August 23, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) N/A 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: **N/A**

- 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? **N/A**
  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: May 29, 2007

NDA #: 21-964

DRUG NAMES: Methylnaltrexone Bromide Injection

APPLICANT: Progenics Pharmaceuticals, Inc.

BACKGROUND: NDA 21-964 provides for Methylnaltrexone Bromide Injection for the treatment of opioid-induced constipation in patients receiving palliative care. Methylnaltrexone Bromide is a new molecular entity and this application has been assigned a standard review classification. The user fee due date is January 30, 2008. This application is completely electronic and has been submitted in the electronic common technical document format.

An end-of-phase 2 meeting was held on July 10, 2003. A follow-up teleconference regarding a thorough QT study was held April 1, 2004. A CMC pre-NDA meeting was held November 1, 2004. A clinical and non-clinical pre-NDA meeting was held August 15, 2005 and a follow-up biopharmaceutics teleconference was held August 31, 2005. A final CMC pre-NDA meeting was held August 23, 2006.

ATTENDEES:

Attendee	Title	Division/Office
Julie Beitz, M.D.	Director	Office of Drug Evaluation III
Joyce Korvick, M.D.	Acting Director	Division of Gastroenterology Products
Mike Welch, Ph.D.	Team Leader, Biometrics	Division of Biometrics V
Sonia Castillo, Ph.D.	Mathematical Statistician	Division of Biometrics III
Kate Dwyer, Ph.D.	Mathematical Statistician	Division of Biometrics III
Sushanta Chakder, Ph.D.	Pharm/Tox Reviewer	Division of Gastroenterology Products
Tamal Chakraborti, Ph.D.	Pharm/Tox Reviewer	Division of Gastroenterology Products
Marie Kowblansky, Ph.D.	Pharmaceutical Assessment Lead	Office of New Drug Quality Assurance
Jane Chang, Ph.D.	Review Chemist	Office of New Drug Quality Assurance
Sue Chih Lee, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics	Division of Clinical Pharmacology III
Tapash Ghosh, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer	Division of Clinical Pharmacology III
Khairy Malek, M.D.	Medical Officer	Division of Scientific Investigations
Vinayak Pawar, Ph.D.	Microbiology Reviewer	Office of Pharmaceutical Science
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff	Division of Gastroenterology Products

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

Discipline/Organization	Reviewer
Medical:	Ron Orleans, M.D.
Secondary Medical:	Fathia Gibril, M.D.
Statistical:	Kate Dwyer, Ph.D.
Pharmacology:	Tamal Chakraborti, Ph.D.
Statistical Pharmacology:	Sushanta Chakder, Ph.D.
Chemistry:	Jane Chang, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Tapash Ghosh, Ph.D.
Microbiology, sterility:	Vinayak Pawar, Ph.D.
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Khairy Malek, M.D.
OPS:	N/A
Regulatory Project Management:	Brian Strongin, R.Ph., M.B.A.
Other Consults:	DDMAC (Michael Brony) DMETS

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: eCTD format

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.

Brian Strongin, R.Ph., M.B.A.
Regulatory Project Manager

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):

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):

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").

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 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)). YES ☐ NO ☐

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

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).

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):

☐ 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):

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) 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*

  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

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

/s/

Brian Strongin
6/1/2007 10:37:20 AM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: May 31, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Gary Della'Zanna, D.O, Director, Division of Scientific Investigations, HFD-45

From: Brian Strongin, Chief, Project Management Staff, HFD-180
Division of Gastroenterology Products

Subject: **Request for Clinical Site Inspections**
NDA 21-964
Progenics Pharmaceuticals, Inc.
(Methylnaltrexone) Injection

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects Treated	Indication
13	MNTX 301	27	Treatment of Opioid-Induced Constipation
07	MNTX 301	24	Treatment of Opioid-Induced Constipation
24	MNTX 302	18	Treatment of Opioid-Induced Constipation
11	MNTX 302	14	Treatment of Opioid-Induced Constipation

27	**MNTX 302**	**12**	**Treatment of Opioid-Induced Constipation**

Domestic Inspections:

We have requested inspections because (please check all that apply):

__X__ Enrollment of large numbers of study subjects

__X__ High treatment responders (specify:)

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 30, 2007. We intend to issue an action letter on this application by (division action goal date) January 30, 2008. The PDUFA due date for this application is January 30, 2008.

Should you require any additional information, please contact Brian Strongin, R.Ph., M.B.A..

Concurrence: (if necessary)

Fathia Gibril, M.D., Medical Team Leader
Ron Orleans, M.D., Medical Reviewer

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

/s/

Brian Strongin
6/1/2007 01:39:39 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: May 31, 2007

To: Alexander Rochefort	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Progenics Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: (914) 784-1872	**Fax number:** (301) 796-9905
Phone number: (914) 784-1881	**Phone number:** 301-796-1008

Subject: Biopharm Information Request, NDA 21-964 Methylnaltrexone Injection

Total no. of pages including cover: 3

Comments:

Please respond to the attached information requests as soon as possible. Thank you.

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2130. Thank you.

Regarding NDA 21-964 Methylnaltrexone Injection:

Please provide documentation, or the location of the documentation in the NDA, for the agreement between Progenics and the FDA to allow the submission of the final report of study 3200K1-103-US with the 120-day safety update.

Thanks.

Appears This Way
On Original

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

/s/

Brian Strongin
5/31/2007 03:43:05 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-964

NDA ACKNOWLEDGMENT

Progenics Pharmaceuticals, Inc.
Attention: Alexander W. Rochefort
Senior Director, Regulatory Affairs
Old Saw Mill River Road
Tarrytown, New York 10591

Dear Mr. Rochefort:

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

Name of Drug Product: Methylnaltrexone Injection

Review Priority Classification: Standard (S)

Date of Application: March 30, 2007

Date of Receipt: March 30, 2007

Our Reference Number: NDA 21-964

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 May 29, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 30, 2008.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred 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 Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
5/14/2007 04:36:23 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 15, 2005

Time: 11:30-1:00 PM

Location: Parklawn Building, Potomac Conference Room

Application: IND 64,583

Type of Meeting: Pre-NDA, Type B

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Florence Houn, M.D.	Office Director, CDER, ODE III
Brian Harvey, M.D., Ph.D.	Division Director
Ruyi He, M.D.	Medical Team Leader
Eric Brodsky, M.D.	Medical Reviewer
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Stella Grosser, Ph.D.	Statistical Team Leader
Zei-Pao Huang	Review Support
Sue-Chih Lee, Ph.D.	Biopharm Review
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Progenics Pharmaceuticals, Inc.

Dr. Thomas Boyd	Vice President, Preclinical Development & Project Management
Dr. Harold Doshan	Clinical P.D. & P.K.
Dr. Robert Israel	Senior Vice President, Medical Affairs
Dr. Alton Kremer	Vice President, Clinical Research
Dr. Paul Maddon	Chairman and CEO
Alexander Rochefort	Director, Regulatory Affairs
Nancy Stambler	Director, Biometrics
	Medical Director,
	Consultant, Statistics

Background:

On June 2, 2005, the Sponsor requested a pre-NDA meeting for the purpose of obtaining the agreement on their proposed content and format of the Clinical, Non-Clinical and Package Insert sections of the Methylnaltrexone (MNTX) Injection NDA.

The sponsor plans to submit their NDA first quarter, 2006.

A subsequent July 15, 2005 background package was submitted, which contained 16 questions for discussion.

Following introductions, the Sponsor agreed to proceed directly to the questions for discussion.

Discussion Points: (bullet format):

Non-Clinical

8.1 Does FDA agree that the non-clinical (Module 4) studies listed in this briefing document are sufficient to support the NDA?

FDA Response:

Yes.

8.2 As recommended by FDA at the End-of-Phase 2 meeting on July 10, 2003, we conducted studies in the manner of Carlsson et al. We consider the completed studies to be sufficient to address the preclinical characterization of possible QT interval effects. Does the Agency agree?

FDA Response:

No. Although the testing program is incomplete, the completed studies do identify the risk of QT-prolongation.

8.3 As agreed at the End-of-Phase 2 meeting on July 10, 2003, pharmacokinetics bridging data have been generated in animals to support the use of intravenous toxicology studies in the NDA for the subcutaneous product. The data will be included in the NDA. Does the Agency agree that these data will be sufficient to support the NDA?

FDA Response:

Yes.

8.4 Does the Agency agree that the requirement for drug-drug interaction studies is adequately addressed by the preclinical studies described in the briefing package, and that human clinical studies are not necessary?

FDA Response:

- ***In vitro* studies have shown that methylnaltrexone is a CYP2D6 inhibitor. Depending on the concentrations observed with the therapeutic doses, in vivo drug-drug interaction studies with CYP2D6 substrates likely to be co-administered in the patient population may be necessary.**
- **Additionally, *in vitro* studies should be conducted to evaluate methylnaltrexone as a CYP inducer. Positive *in vitro* study results can trigger the need for *in vivo* studies.**
- **It is indicated in the submission that elimination of methylnaltrexone is primarily via renal excretion. Address drug-drug interaction potential with other renally eliminated drugs.**

8.5 Our NDA specification for MNTX drug substance will include a limit for the process impurity This process impurity was qualified in a number of studies including the 90-day rat and dog IV toxicology studies. Does the FDA agree that this process impurity is adequately qualified?

FDA Response:

No. The results of toxicology studies support the safety of the impurity up to a level of only. You need to in order to qualify or conduct the following studies with

1. **Ames test**
2. **Chromosome aberration assay with human lymphocytes**
3. **14-day repeated dose intravenous toxicity study in rats**

Please refer to "ICH Q3A. Guidance on Impurities in New Drug Substances, February 2003".

In addition, you should also determine the level of an impurity in This impurity is likely to be carried over into the The qualification threshold for potential mutagenic impurities in opioids is if the daily dose of opioid is up to mg/day. As the recommended dose of MNTX is mg/kg, the daily dose would be mg/day based on a 50-kg body weight. If the impurity is present above this threshold level you need to conduct the following genotoxicity studies with since it is a known structural alert for genotoxicity:

a. **Ames test**
b. **Chromosomal aberration assay in human lymphocytes**

If the genotoxicity assay yields a positive result, the specification for the impurity should be lowered to no more than (NMT) or the impurity should be adequately qualified via a carcinogenicity assessment in a single species.

Meeting Update

- *The sponsor proposes to impurity to*
- *We agreed to the levels of impurity at the pre-NDA CMC meeting (November 1, 2004).*

Clinical

8.6 Does the FDA agree that the clinical studies provided in Tables 1 and 2 in Section 9.2 in conjunction with summary safety information from the literature are sufficient to support the NDA?

FDA Response:

The clinical studies provided in Tables 1 and 2 in Section 9.2 in conjunction with summary safety information from the literature may be sufficient to support filing of a NDA.

However, we are concerned about the ability of the data to support approval; specifically, the data needed to support the dosing and administration section in the proposed label. We understand that methylnaltrexone (MNTX) Bromide may be administered up to as needed, at doses of However, the duration of treatment in the double-blind, randomized portion of study 301 is one dose and in study 302 the duration is two weeks. At this point, it is not clear how the additional, non-randomized data would be used to support the ' statement in your labeling, and what you would have physicians and patients do after the

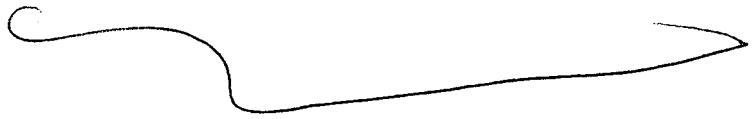
In addition, your proposed NDA for the treatment of OIC in the terminal ill patients has the following efficacy concerns:

1. **All of the efficacy endpoints may be confounded by the amount of opioids (in morphine equivalents). If the amount of opioids in the study is not balanced, then this may need stratification.**

2. **The statistical analysis plan's (SAP) use of the last value carried forward (LVCF) method may bias the evaluation of drug efficacy.**

3. **Your efficacy endpoints lack adequate evaluation of straining, spontaneity (SBM), frequency, and consistency or completeness of BMs (CBMs). No efficacy endpoint compares the frequency of BM/week, SBM/week, or CSBM/week compared to baseline. However, we do understand it is difficult**

to evaluate some of these endpoints in your proposed terminal ill population.



Finally, we request more detailed information on the study population. Please provide us frequency distribution of patient diagnoses and morphine equivalents by treatment arm and survival curves by treatment arm.

8.7 As agreed at our End-of-Phase 2 meeting, the NDA will include results from two double-blind, randomized, parallel-group, multi-center, placebo-controlled phase 3 trials (MNTX 301 and MNTX 302). Our analysis of the first trial, MNTX 301, was highly significantly positive. Assuming our second phase 3 study (MNTX 302) is also positive, does the Agency agree that these studies are sufficient to demonstrate efficacy in the claimed indication?

FDA Response:

Based on current available data, it is premature to answer this question. Efficacy evaluation is data dependent.

We have the following concerns regarding the design of Study 301:

1. **The allowance of rescue laxatives up to 4 hours prior to study during drug administration may confound the results.**
2. **The eligibility criteria may not adequately select patients who have OIC. It is possible for a patient to be on 5 mg of oxycodone, a stool softener, and not have significant laxation for 48 hours and still be entered into this trial. In this example, this patient may not have OIC.**
3. **Please clarify the time frames of secondary efficacy endpoints including: the change in constipation distress, consistency, difficulty, opioid withdrawal, and pain scores. Are these changes derived from the 24-hour time point and/or the 4-hour time point compared to the baseline time point?**

We have the following concerns regarding the design of Study 302:

1. **The lack of standardization of efficacy results may impair the efficacy evaluation. The definition of laxation within four hours of study drug administration (a positive response) was not pre-specified in the protocol for the 2 primary and 7 secondary efficacy endpoints.**

2. **The primary endpoints do not evaluate the efficacy of the second week of the study.**

3. **It is possible for a patient to achieve both co-primary endpoints and have worse OIC after one week of therapy compared to their baseline.**

4. **The allowance of rescue laxatives up to 4 hours prior to study drug administration may confound the results of co-primary endpoints about the first dose.**

5. **The efficacy endpoints may be confounded by the amount of opioids (in morphine equivalents). If the amount of opioids in the study is not balanced, then this may need stratification. Since the protocol did not require "stable" baseline dosing, the amount of opioids administered during at least three days prior to study drug use will be needed.**

6. **The statistical analysis plan's (SAP) use of the last value carried forward (LVCF) method may bias drug efficacy evaluation.**

The Agency recommends that to support prn use in terminally ill patients with opiod-induced constipation:

***1) Every other day dosing prn use should be studied for at least 1 month.**

2) Additional daily dosing information may be needed to ensure safety.

Please provide exposure profile (dosing, duration) in your 3 months 301EXT and 302EXT Studies. Provide rationale for QD use.

Meeting Update

****For clarification, 1) Every other day dosing prn use should be studied for at least 1 month has been changed to read the following:***
Prn dosing to a maximum of once per day should be studied for at least 1 month.

8.8 As agreed at our End-of-Phase 2 meeting, the NDA safety database will consist of Progenics' MNTX studies and a summary of the University of Chicago MNTX studies from the literature. Specifically, the NDA safety database will consist of approximately 317 AMI patients (274 MNTX and 107 placebo); 354 volunteers/patients from other Progenics-sponsored MNTX studies (275 MTNX and 79 placebo), and MNTX summary safety information including 433 University of Chicago volunteers/patients (337 MNTX and 96 placebo). Does the FDA have any comments on the proposed safety database?

FDA Response:

We are unable to answer this question without additional safety exposure information. Please provide the number of AMI patients; volunteers/non-AMI patients; and Chicago University volunteers/patients who will receive 0.15 mg/kg or more of SC/IV MNTX and 0.3 mg/kg or more of SC/IV MNTX in your completed trials for the NDA. Provide the frequency distribution of duration of exposure for each of the six groups. Also provide the frequency distribution of the duration of exposure of AMI patients to the above dose groups in controlled studies.

8.9 As agreed at the End-of-Phase 2 meeting, we will submit the results of PK studies in hepatic and renal impairment. In addition, as outlined in this briefing document, the NDA will contain PK data from healthy volunteers, including cold & radio-tagged studies, and a cardiac QTc study. Does FDA agree that the NDA has sufficient PK information?

FDA Response:

It appears that you may not have all of the studies that are needed for NDA submission, based on the limited information provided in the package.

- **Multiple dose PK data are required. It's unclear whether PK data were collected in the multiple-dose study (Study 251).**
- **In addition, the Agency will expect PK data related to age, gender and race.**
- **There are no studies in end-stage renal impairment patients requiring dialysis. This fact will be reflected in the label.**

Meeting Update

There will be further discussion between the Biopharm Team Leader, Reviewer and Sponsor regarding the specific requirements to address the biopharm issues.

8.10 As agreed at our End-of-Phase 2 meeting, special population studies were conducted in renally and hepatically impaired subjects. In addition, as agreed during our April 1, 2004 meeting, a study was performed to assess QTc interval effects. Does the Agency agree that these special population studies are sufficient to support the NDA?

FDA Response:

There are no studies in end-stage renal impairment patients requiring dialysis. This fact will be reflected in the label. (See response to Question #8.9.)

8.11 The first phase 3 study and the extension to this study (MNTX 301EXT) were conducted under separate protocols. As both of these studies shared the same patients, investigators, and clinical vial labeling, we propose to report MNTX 301 and MNTX 301EXT in one study report in the NDA. Does the Agency agree with this approach?

FDA Response:

This is acceptable. However, you need to provide separate safety and efficacy tables for the double-blind and open-labeled portions.

8.12 Progenics plans to conduct pediatric studies post-approval and Appropriate juvenile toxicology studies are being planned, to be followed by pediatric clinical studies. FDA guidance will be sought in the development of this pediatric development plan. Therefore, Progenics respectfully requests a

deferment of pediatric assessment for our initial MNTX NDA as per 21CFR 314.55 (b). Does FDA agree to grant the deferment?

FDA Response:

Yes. This is acceptable. Furthermore, this request should also be made within the NDA submission. Please provide your pediatric plan within the submission.

8.13 We plan to submit SAS data sets (CDISC format) for the MNTX Injection NDA clinical studies, in lieu of patient listings/diaries. Does FDA agree with this approach?

FDA Response:

A set of Blank_CRF with field mapping and detailed define.pdf are essential to our reviewers. Please follow the CDISC implementation guidance.
The link to the implementation guide is:

http://www.cdisc.org/models/sds/v3.1.1/index.html

The datasets should not be over 50MB in size.

8.14 Our MNTX Injection NDA is being prepared as a hybrid e-NDA, following CTD format. We are working with [redacted] to publish the MNTX Injection hybrid e-NDA, CTD format. Does the Agency have any comments/suggestions regarding receiving our MNTX Injection NDA as e-NDA hybrid, CTD format, submission, including the early [up to 120 days prior - CFR 314.50 (d)(1)(iv)] submission of the CMC section?

FDA Response:

It is acceptable to send the submission as a hybrid eCTD.

8.15 The NDA will be in CTD format including the CTD clinical summary and overview identified in the CTD guidance documents. We do not plan to provide additional clinical summary NDA documents in the ISS and ISE formats. Does the Agency agree with this approach?

FDA Response:

No. The ISS summaries are required. However, you do not need to provide the ISE summary. Provide all safety tables for three groups: the AMI population, the non-AMI population, and the total population.

8.16 A draft PI is provided in this briefing document. From the information provided does the FDA have any comments/suggestions regarding the draft PI?

FDA Response:

We cannot at this time comment on the draft PI as the PI is derived from the safety and efficacy data in the NDA. However we have the following initial comments/suggestions:

1)

2) The population (terminal AMI patients) should be further defined in the CLINICAL STUDIES section.

Additional clinical comments/questions:

- **Clarify if laxatives were allowed to be administered 4 to 24 hours after the first study dose in Study 302.**
- **When will the final report for Study 302EXT be available?**
- **To improve the efficiency of the clinical review of your NDA please provide all of the relevant information especially the safety information according to MAPP 6010.3 (Clinical Review Template at www.fda.gov/cder/mapp/6010.3.pdf) in your NDA submission.**
- **Please clarify the secondary endpoints in Study 251:**
  - **Are the frequency, consistency, and difficulty of BMs for the double-blind portion of the trial during week 1 compared to the baseline period?**
  - **Does "Week 1" represent Day 7 or the post-dose Day 5 efficacy assessment for the 10 secondary endpoints in the double-blind portion of the trial?**

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/s/

Tanya Clayton
9/13/2005 03:48:42 PM

Ruyi He
9/13/2005 05:27:51 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 1, 2004

TIME: 12:00 PM – 1:30 PM

LOCATION: Parklawn Building, 6B-45 Conference Room (Teleconference)

APPLICATION: IND 64,583
Methylnaltrexone (MNTX) Injection

TYPE OF MEETING: Type B: Pre-NDA meeting

MEETING CHAIR: Dr. Ray Frankewich

MEETING RECORDER: Mr. Ryan Barraco

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Joyce Korvick, M.D., M.P.H	Acting Division Director	Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)
2. Ryan Barraco	Consumer Safety Officer	DGCDP (HFD-180)
3. Eric Duffy, Ph.D.	Director	Division of New Drug Chemistry II (DNDCII) (HFD-820)
4. Blair Frasier, Ph.D.	Deputy Director	DNDCII (HFD-820)
5. Liang Zhou, Ph.D.	Chemistry Team Leader	DNDCII (HFD-820)
6. Ramesh Raghavachari, Ph.D.	Chemist	DNDCII (HFD-820)
7. Ray Frankewich, Ph.D.	Chemist	DNDCII (HFD-820)

EXTERNAL CONSTITUENT (Progenics Pharmaceuticals, Inc.) ATTENDEES AND TITLES:

External Attendee	Title	Representing
Thomas Boyd, Ph.D.	Vice President, Preclinical Development & Project Management	Progenics Pharmaceuticals, Inc.
Richard Czarnecky	Director, Quality	Progenics Pharmaceuticals, Inc.
Suzette Dowling	Associate Director, Regulatory Affairs	Progenics Pharmaceuticals, Inc.
Tony Komotar	Senior Manager, Contract Manufacturing	Progenics Pharmaceuticals, Inc.
Meryl Longval	Director, Materials Management	Progenics Pharmaceuticals, Inc.
Paul Maddon, M.D., Ph.D.	Chairman and CEO	Progenics Pharmaceuticals, Inc.
Julio Perez, Ph.D.	Senior Manager, Pharmaceutical Chemistry	Progenics Pharmaceuticals, Inc.
Nitya Ray, Ph.D.	Vice President, Manufacturing	Progenics Pharmaceuticals, Inc.
Alexander Rochefort	Senior Director, Regulatory Affairs	Progenics Pharmaceuticals, Inc.
Diana Trumbley	Senior Manager, Quality	Progenics Pharmaceuticals, Inc.
	Consultant	
	Consultant	

BACKGROUND:

Progenics Pharmaceuticals, Inc. submitted a Meeting Request (MR) on August 4, 2004, received August 5, 2004, for a Pre-NDA meeting for Methylnaltrexone (MNTX) Injection. The sponsor submitted 14 questions addressed to the Agency. The sponsor requested the Pre-NDA meeting to obtain Agency agreement on the proposed content and format of the Chemistry, Manufacturing and Controls (Quality) section of the MNTX Injection e-NDA, CTD hybrid format, to be filed in the second half of 2005.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the sponsor's background package, submitted September 30, 2004.

DISCUSSION POINTS:

In response to the sponsor's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the sponsor's questions, followed by the Agency's responses in bold lettering.

IND # 64,583
Methylnaltrexone (MNTX) Injection
Pre-NDA CMC Meeting - November 1, 2004

Drug Substance - Manufacture

1. The drug substance commercial manufacturing process is being scaled up after phase 3 studies from ——— Kg per batch, at the same manufacturing site. Does the Agency agree with our plan to provide data in the NDA to commercialize both batch sizes?

Agency Response:

- **Your proposal appears to be acceptable. Provide data for drug substance batches for both clinical and commercial processes for comparison.**
- **Please identify and describe the critical manufacturing process control(s) when the NDA is submitted.**

Drug Substance - Control of Starting Material

2.

Agency Response:

- **Consistent with our recommendations for other drug products with this problem, a threshold with NMT ——— would be acceptable on an interim basis with a timeline to achieve NMT ——— as the target specification. You should provide a timeline for achieving the NMT ——— acceptance criterion.**
- **Please be advised that we do not consider ——— a starting material for the synthesis of the drug substance.**

Drug Substance - Control

3. Does the Agency agree with our proposed lot release testing for drug substance? Justification for acceptance criteria will be provided in the NDA and in Mallinckrodt's Type II Drug Master File (DMF # [redacted]

Agency Response:

- **Release specification should be considered an in-house specification. Appropriate acceptance criteria for both impurities and degradation products (both specified and unspecified) should be provided and justified. Refer to ICH Q6A and Q3A. It is recommended that the regulatory specification include references (including code numbers) to analytical procedures. It is recommended that acceptance criteria for impurities and residual solvents should be tightened according to batch analysis data.**

- **You should propose an acceptance specification for the drug substance (e. g. assay, impurities, appearance, etc.).**

4. Will the Agency accept reference to Mallinckrodt's DMF for the analytical methods validations information?

Agency Response:

- **Refer to response for number 3. Validation data for analytical procedures should be included in the NDA. However, we will accept a reference to Mallinckrodt's DMF.**

Drug Substance - Stability

5. Does the Agency agree with the adequacy of our drug substance stability plan for marketing approval?

Agency Response:

- **Your proposal for reporting stability data appears to be acceptable. Please refer to response for question no. 1. Drug substance retest date will be determined during NDA review.**

6. Will the Agency accept a summary of stability data in the NDA and reference to Mallinckrodt's DMF for complete stability data?

Agency Response:

- **We recommend that stability data should also be provided in the NDA. This data may be provided to you by the DMF holder (for convenience of review). We will accept a reference to Mallinckrodt's DMF.**

Drug Product - Pharmaceutical Development - Closure Change

7. The commercial process will use a modified version of the vial stopper used in phase 3 clinical studies. The stopper supplier advised us that the [redacted] of the vial stopper was modified. [redacted] Does the Agency agree with our plan to provide data in the NDA to support the use of [redacted] vial stoppers?

Agency Response:

- **Your plan to provide data in the NDA to support the use of [redacted] vial stoppers appears to be acceptable.**

8. The contract manufacturer, [redacted] is considering [redacted] Does the Agency agree with our proposal to submit this change as a post-approval "Changes Being Effected" Supplement?

Agency Response:

- **If the materials used to make or treat the stoppers are changed, a prior-approval supplement would be required (please refer to the guidance titled, "Changes to an Approved NDA or ANDA Questions and Answers"). If the stopper is the same, a CBE-0 is acceptable.**

Drug Product Manufacture

9. Will the Agency accept a summary of [redacted] process validation in the NDA and reference to DSM's Type V Drug Master File (DMF [redacted] for complete validation data?

Agency Response:

- **At this time, this proposal appears to be acceptable. Please communicate with both the microbiology review division and your FDA district office regarding any concerns with [redacted] process validation. Please be advised that a DMF containing information describing the manufacture of a drug product should be a Type II DMF.**

- **The sponsor clarified that the data in question is not product specific and therefore the Agency agrees that a Type V DMF is an appropriate reference.**

10. Progenics is planning to [redacted]

Does the Agency agree with our plan?

Agency Response:

- **Please refer to response of Question #9. Please consult with your FDA district office regarding the proposed commercial process validation study.**

- **Please identify and describe the critical manufacturing process control(s) for the drug product, when the NDA is submitted.**

Drug Product Control

11. Does the Agency agree with our proposed lot release testing for drug product? Justification for acceptance criteria will be provided in the NDA.

Agency Response:

- **Release specification should be considered an in-house specification. Provide appropriate acceptance criteria for impurities (both specified and unspecified) for both impurities and degradation products as appropriate. Refer to ICH Q6A and Q3B. It is recommended that the regulatory specification include references (including code numbers) to analytical procedures. It is recommended that acceptance criteria for impurities should be tightened according to batch analysis data. Endotoxin limits should be justified based upon maximum dose.**

Drug Product Stability

12. Does the Agency agree with the adequacy of our stability plan for marketing approval and commitment?

Agency Response:

- **It appears that the plan for submission of drug product primary stability data is acceptable.**

General

13. Does the Agency agree with Progenics' proposal to claim a categorical exclusion for the environmental assessment reporting requirement based on the Expected Introduction Concentration (EIC) being less than 1 ppb?

Agency Response:

- **This appears to be acceptable.**

14. Does the Agency agree with our plan to submit an e-NDA CTD hybrid [redacted] format filing following CTD Module 3 contents and draft FDA NDA drug substance and drug product guidance documents for [redacted] of the CMC section?

Agency Response:

- **This appears to be acceptable. Contact the Office of Information Technology, Review Technology Staff regarding any concerns regarding electronic submission and quality.**

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/s/

Ryan Barraco
11/30/04 10:43:37 AM

Ray Frankewich
11/30/04 10:59:17 AM

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 10, 2003

Time: 2:00-3:30 PM

Location: Parklawn Building, 3rd Floor, "Potomac" Conference Room

Application: IND 64,583

Type of Meeting: IND

Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., M.S.	Division Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical (GI) Team Leader
Ann Marie Trentacosti, M.D.	Medical Reviewer
Lian Zhou, Ph.D.	Chemistry Team Leader
Ramesh Raghavachari, Ph.D.	Chemistry Reviewer
Jasti Choudary, B.V.Sc., Ph.D.	Supervisory Pharmacologist
Milton Fan, Ph.D.	Statistician
Alice Kacuba, M.S.N., R.N., RAC	Regulatory Health Project Manager
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Thomas Boyd, Ph.D.	Vice President, Preclinical Development and Project Management
Harold Doshan, Ph.D.	Drug Metabolism and Pharmacokinetics, Medical Affairs
Frank Galasso, M.S.	Clinical Project Manager, Medical Affairs
Robert Israel, M.D.	Senior Vice President, Medical Affairs
Paul Maddon, M.D., Ph.D.	Chairman and CEO
Nancy Stambler, M.S.	Director, Biometrics
Kenneth Surowitz, Ph.D.	Vice President, Regulatory Affairs and Quality

Background:

Methylnaltrexone Injection is being developed as a treatment of [redacted] constipation in patients with advanced medical illness receiving opioids. On May 9, 2003, the firm requested a meeting for the purpose of updating the Agency on the Phase 2 results, presenting the updated design of the second Phase 3 study (MNTX 302) and getting the Agency's input on the final content of the preclinical and clinical packages for the proposed NDA.

A subsequent June 17, 2003 background package was submitted, which contained 8 questions.

Discussion Points: (bullet format):

1. In response to the suggestions of the Agency at our previous meeting, we have modified the design of Studies MNTX 301 and MNTX 302. Does the Agency agree that these studies constitute the pivotal clinical trials for marketing approval for the proposed indication?

   - **Yes, the design of studies 301 and 302 is adequate for Phase III evaluation.**

2. Progenics does not plan to conduct special studies in subjects with renal or hepatic impairment. In addition, we would like to request a waiver from studies in pediatric subjects. Does FDA agree with this approach?

   - **This is not acceptable. The Clinical Pharmacology & Biopharmaceutics section should be complete at the time of NDA submission. Studies in patients with renal or hepatic impairment are needed, especially because the target population includes ill patients who may already have renal or hepatic impairment.**

   - **The Sponsor will submit protocols for these studies and the Agency will provide feedback.**

3. The plan for the comprehensive NDA Safety Database is outlined in Section 9F of the Briefing Book. Does FDA agree with this approach?

   - **This approach appears to be acceptable.**

4. Based upon input from the Agency at the November 2002 meeting, we have amended the design of study MNTX 302 to encompass a 2-week duration of blinded treatment. In addition, we have incorporated the modified Rome criteria as a secondary endpoint (greater

than or equal to 3 bowel movements per week). If this endpoint is achieved, we would plan to seek guidance from the Agency on a label for treatment of constipation. Please comment.

- **This indication under consideration is constipation. A more appropriate indication would be treatment of opioid induced constipation. The proposed studies**

5. In response to FDA's request to conduct studies on acute toxicity, we have conducted additional studies and believe that our toxicology database adequately defines the acute toxicity of the compound in animals. Does FDA agree?

   - **No single toxicity studies are available and acute toxicity has not been defined. However, since you have 90 day IV toxicity studies, single dose studies are no longer required.**

6. In response to the Agency's request to conduct additional mutagenicity studies, we conducted an additional study and believe, in view of the lack of genotoxic effect of MNTX in four studies, that these studies adequately address genotoxicity. Does FDA agree?

   - **Please conduct the studies as recommended in the minutes of the November 13, 2002 meeting.**

7. Progenics has completed additional preclinical cardiovascular studies requested by FDA. We further plan to conduct cardiac monitoring of human subjects in MNTX 102 and in other studies. Does FDA agree with this approach?

   - **Please conduct the other studies as recommended in the reference cited in the minutes of the November 13, 2002 meeting.**

Additional Questions

1. We believe there are no issues regarding comparative drug distribution or absorption between our current and proposed sterilized MNTX product, since both formulations are true solutions.

   A. Does FDA agree that a determination of bioequivalency would not be necessary between the two formulations?

   B. Would bioequivalency need to be established if Progenics switched to a different manufacturer for the sterilized product than used for the processed formulation?

2. Progenics has just begun a first Phase 3 study with the [redacted] formulation. A second Phase 3 study will be necessary before our NDA is submitted.

   A. Is there any need to include the [redacted] sterilized [redacted] formulation in the second Phase 3 clinical study (or in part of the study) in the planned NDA?

   B. Would it be sufficient to qualify the [redacted] formulation by including the formulation stability and sterility of marketing batches as documentation in the NDA?

   - **You should contact Microbiology directly regarding responses to Additional Questions 1 (A and B) and 2 (A and B).**
   - **In addition, please submit an amendment providing a large picture of the development plan and how the component changes will affect the larger picture such as potential increase in impurities.**
   - **After that, if questions remain, a meeting can be requested.**

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/s/

Hugo Gallo Torres
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/s/

Tanya Clayton
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