MEMORANDUM

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

DATE: April 23, 2008

TO: Review #1 of NDA 21-964

FROM: Jane Chang
Review Chemist, ONDQA

SUBJECT: Labeling Review
NDA 21-964
Relistor (MethylNaltrexone Bromide) Subcutaneous Injection

SUMMARY

After completion of CMC Review #1, revised labeling information for package insert and immediate container and carton were provided by the applicant via emails and found to be acceptable. Additional recommendation for Drug Listing Data Elements in Structured Product Labeling was also conveyed to the applicant via email.

RECOMMENDATION

This NDA may be approved from a chemistry, manufacturing, and controls review perspective.

(See attached electronic signature page)

Jane L. Chang, Ph.D.
Review Chemist

(See attached electronic signature page)

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

Date
6 Page(s) Withheld

X Trade Secret / Confidential

Draft Labeling

Draft Deliberative Process

Withheld Track Number: Chemistry
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Jane Chang
4/23/2008 05:27:10 PM
CHEMIST

Moo-Jhong Rhee
4/23/2008 05:32:25 PM
CHEMIST
Chief, Branch III
**Relistor**  
(Methylnaltrexone Bromide)  
Injection

**NDA 21-964**

Division Director Review  
Chemistry, Manufacturing, and Controls

**Applicant:** Progenics Pharmaceuticals, Inc.  
777 Old Saw Mill River Road  
Tarrytown, NY 10591

**Indication:** Treatment of opioid-induced constipation in patients receiving palliative care

**Presentation:** Relistor Injection is supplied as a single strength, sterile, 20 mg/mL solution of methylnaltrexone bromide. Each single-use, 3 mL glass vial contains 12 mg of methylnaltrexone bromide, 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride in 0.6 mL of solution. One vial per carton or one vial per tray (packaged with syringe and swabs).

**EER Status:** Acceptable  5-JUL-2007

**Consults:**  
Microbiology – Approval  30-NOV-2007  
EA – Categorical exclusion granted under 21 CFR §25.31(b)  
Methods Validation – Revalidation by Agency not requested

**Original Submission:** 30-MAR-2007

**Post-Approval Agreements:** None

**Drug Substance:**

Methylnaltrexone bromide is a chiral derivative of naltrexone, the opioid receptor antagonist, and is a small, synthetic, New Molecular Entity (NME) with an empirical formula of C₂₁H₂₆NO₄Br and a molecular weight of 436.36. Known chemically as (R)-N-(cyclopropylmethyl)noroxyxomorphone methobromide, it exists as a white to faint gray, crystalline powder with a melting point of 485°C. Methylnaltrexone bromide is soluble in water (300 ng/mL) and aqueous buffers (pH 1.0 to 12.0), has a pKa of 8.4, and is very slightly soluble in alcohols. Its partition coefficient (log P) in human livers is consistently produced by the commercial manufacturing process and is considered the stable form of the drug substance.
The bulk drug substance is manufactured by Mallinckrodt, Inc., St. Louis, Missouri. The chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, is described in Mallinckrodt’s Type II DMF... has been reviewed, and is concluded to be adequate. A summary description of the manufacturing process was provided in the application.

The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The impurities and degradants have been investigated. The primary reference standard for drug substance, manufactured by the commercial process, and reference standards for specified impurities have been characterized by the proposed regulatory methods as well as by additional methods.

The stability data for three commercial batches support a / month retest period for the bulk drug substance stored either inside an bags contained in containers with lids at controlled room temperature, 25±2°C / 60%RH.

**Conclusion:** Drug substance is acceptable.

**Drug Product:**

Relistor is supplied as a single-use, sterile, solution of (allowing withdrawal of 0.6 mL) in a nominal 3 mL clear, Type I, glass vial sealed with a gray rubber stopper with plug and oversealed with an aluminum, flip-top cap.

Each vial of Relistor contains 20 mg/mL methylhexatrexone bromide mg/mL sodium chloride USP, mg/mL edentate calcium disodium USP, and mg/mL glycine hydrochloride, adjusted to pH 3.0 to 5.0 with USP and USP, in Water for Injection USP. Glycine hydrochloride is manufactured under cGMP using...
USP. The formulation is into vials by

Specification of the drug product includes: appearance, clarity, identification by HPLC and UV spectrophotometry, strength by HPLC, degradants and impurities by HPLC, volume in container, pH, particulate matter, edentate calcium disodium, sterility, and bacterial endotoxins. Reference standards for drug product impurities were developed for use in validating analytical methods. All test methods have been appropriately validated for their intended purpose.

Sufficient stability data for three commercial-scale batches of drug product support the requested expiry of 24 months when stored at room temperature, 68°-77°F (20°-25°C); excursions permitted to 15-30°C (59-86°F), and protected from light. Do not freeze.

Conclusion: Drug product is acceptable.

Additional Items:

The sponsor committed to

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for Approval, pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Blair Fraser
2/5/2008 03:34:15 PM
CHEMIST
NDA 21-964

Relistor (Methylnaltrexone Bromide) Injection

Progenics Pharmaceuticals, Inc.

Jane L. Chang, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

For Division of Gastroenterology Products
(HFD-180)
# Table of Contents

Table of Contents .................................................................................................................. 2

Chemistry Review Data Sheet................................................................................................. 4

The Executive Summary .......................................................................................................... 8

I. Recommendations .................................................................................................................. 8
   A. Recommendation and Conclusion on Approvability ....................................................... 8
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable .................................................................................. 8

II. Summary of Chemistry Assessments ................................................................................... 8
   A. Description of the Drug Product(s) and Drug Substance(s) ........................................... 8
   B. Description of How the Drug Product is Intended to be Used ....................................... 10
   C. Basis for Approvability or Not-Approval Recommendation ......................................... 11

III. Administrative .................................................................................................................... 11
   A. Reviewer's Signature: electronically signed in DFS ....................................................... 11
   B. Endorsement Block: electronically signed in DFS ......................................................... 11
   C. CC Block: entered electronically in DFS ....................................................................... 11

Chemistry Assessment ............................................................................................................ 12

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data ...... 12

S DRUG SUBSTANCE .............................................................................................................. 12
   S.1 General Information ...................................................................................................... 12
   S.2 Manufacture ................................................................................................................ 13
   S.3 Characterization .......................................................................................................... 17
   S.4 Control of Drug Substance ........................................................................................... 22
   S.5 Reference Standards or Materials ............................................................................... 32
   S.6 Container Closure System .......................................................................................... 33
   S.7 Stability ....................................................................................................................... 33

P DRUG PRODUCT .................................................................................................................... 36
   P.1 Description and Composition of the Drug Product ....................................................... 36
   P.2 Pharmaceutical Development ......................................................................................... 36
   P.3 Manufacture ................................................................................................................ 44
   P.4 Control of Excipients .................................................................................................... 49
   P.5 Control of Drug Product ................................................................................................ 52
   P.6 Reference Standards or Materials ............................................................................... 68
   P.7 Container Closure System .......................................................................................... 69
   P.8 Stability ....................................................................................................................... 72

A APPENDICES ....................................................................................................................... 78

Page 2 of 88
R  REGIONAL INFORMATION .............................................................................................. 78

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ......................... 79
   A. Labeling & Package Insert .................................................................................. 79
      1. Package Insert .............................................................................................. 79
      2. Labels ........................................................................................................... 81
   B. Environmental Assessment Or Claim Of Categorical Exclusion ......................... 84

III. List Of Deficiencies ............................................................................................... 85
Chemistry Review Data Sheet

1. NDA 21-964

2. REVIEW #: 1

3. REVIEW DATE: 04-FEB-2008

4. REVIEWER: Jane L. Chang

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Documents</th>
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<tr>
<td>11/1/2004 Pre-NDA CMC Meeting Minutes</td>
<td>30-NOV-2004</td>
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<tr>
<td>8/15/2005 Pre-NDA Meeting Minutes</td>
<td>13-SEP-2005</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<thead>
<tr>
<th>Submissions Reviewed</th>
<th>Document Date</th>
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<tbody>
<tr>
<td>Original Submission</td>
<td>30-MAR-2007</td>
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<tr>
<td>Correspondence (C)</td>
<td>17-MAY-2007</td>
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<tr>
<td>Amendment (BC)</td>
<td>07-SEP-2007</td>
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<td>Amendment (BC)</td>
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<td>Amendment (BI)</td>
<td>30-NOV-2007</td>
</tr>
<tr>
<td>Amendment (BI)</td>
<td>18-JAN-2008</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

Name: Progenics Pharmaceuticals, Inc.
Address: 777 Old Saw Mill River Road
         Tarrytown, NY 10591
Representative: Alexander W. Rochefort
Telephone: 914-784-1881
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Relistor
   b) Non-Proprietary Name: Methylnaloxone Bromide Injection
   c) Code Name/# (ONDQA only): N/A
   d) Chem. Type/Submission Priority (ONDQA only):
      1) Chem. Type: I
      2) Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: selective mu-opioid receptor antagonist

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 12 mg/0.6 mL (20 mg/mL)

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: ___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ___SPOTS product – Form Completed
    ___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

   ![Methylnaloxone bromide structure](image)

   (R)-N-(cyclopropylmethyl)noroxyomorphone methobromide.
   Molecular formula: C_{21}H_{26}NO_4Br    MW: 436.36 g/mol
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>HOLDER</th>
<th>ITEM REFERENCED</th>
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<td>N/A</td>
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<td>See the 11/30/07 Microbiology Review by V. Pawar</td>
</tr>
</tbody>
</table>

*DMF was referenced in DMF with letter of authorization dated 21-Oct-2007.
**DMF was referenced in DMFs with letter of authorization dated 21-Oct-2007 and 16-May-2003, respectively.

1 Action codes for DMF Table:
   1 – DMF Reviewed.
   Other codes indicate why the DMF was not reviewed, as follows:
   2 – Type 1 DMF
   3 – Reviewed previously and no revision since last review
   4 – Sufficient information in application
   5 – Authority to reference not granted
   6 – DMF not available
   7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
B. Other Documents:

<table>
<thead>
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<th>DOCUMENT</th>
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<td>IND</td>
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18. STATUS:

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<th>DATE</th>
<th>REVIEWER</th>
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<td>Biometrics</td>
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<td>Methods Validation</td>
<td>N/A, according to the current ONDC policy</td>
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<tr>
<td>Office of Drug Safety</td>
<td>Acceptable for &quot;Relistor&quot; as the proprietary name.</td>
<td>8/2/2007</td>
<td>L. Wisniewski, K. Taylor, D. Toyer, C. Holquist</td>
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<tr>
<td>EA</td>
<td>Categorical exclusion (see this review)</td>
<td>10/03/2007</td>
<td>J. Chang</td>
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<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>11/30/2007</td>
<td>V. Pawar</td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-964

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved pending resolution of minor labeling issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product

Relistor (methylaltrexone bromide) Injection, 20 mg/mL, consists of an aqueous solution of methylaltrexone bromide in a clear, Type I glass vial, grey rubber stopper and aluminum overseal with a flip-off cap. The volume of drug product in the vial is in order to assure a volume of 0.6 mL for withdrawal.

The proposed commercial formulation consists of 20 mg/mL methylaltrexone bromide, mg/mL edetate calcium disodium (CaEDTA), mg/mL glycine hydrochloride and mg/mL sodium chloride in Water for Injection.

The product, which is stable at room temperature storage conditions, is filled in single-use vials for subcutaneous administration up to a 0.6 mL volume or 12 mg methylaltrexone bromide per vial.

Commercial manufacture of the product will occur at This facility manufactured the full-scale site-specific primary stability batches. The commercial formulation is the same as the primary registration stability batches.
The proposed drug product specification includes tests for

Stability data were provided for up to 12 months at 25°C/60%RH and 30°C/75%RH, and up to six months at 40°C/75%RH on three production-scale primary stability batches of the drug product using the commercial container closure. Stability data show no loss in potency and no significant changes in impurities, appearance, and pH for packaged product. Vial orientation was not found to have an impact on product quality. Photostability of the drug product using ICH Option 2 light conditions was also studied for one of the three primary stability registration batches in both the exposed and packaged configurations. The results showed that the secondary opaque container protects the drug product from photodegradation.

Linear regression analyses of naltrexone methobromide content predict that it will be maintained within the limit for the proposed expiration period of 24 months. The applicant has committed to

The stability data support the requested expiry of 24 months when stored at room temperature, 68-77°F (20-25°C); excursions permitted to 15-30°C (59-86°F), and protected from light. Do not freeze.

(2) Drug Substance

The active pharmaceutical ingredient, methyl-naltrexone bromide (MNTX), is a new molecular entity. It is a derivative of the opioid receptor antagonist, naltrexone. Methylation of naltrexone base gives the desired R-configuration at the quaternary nitrogen center. The addition of a methyl group at the amine ring nitrogen forms a permanent positive charge and provides the compound with greater polarity and lower lipid solubility. These properties restrict the ability of MNTX to access the central nervous system in humans. Therefore, MNTX is designed to block undesired adverse effects of opioid pain medications, such as constipation, mediated predominately by the peripherally located opioid receptors, while sparing the desired centrally mediated analgesic effect. MNTX provides a specific treatment for opioid-induced constipation.

Commercial manufacture of methyl-naltrexone bromide is conducted at Mallinckrodt Inc., St. Louis, Missouri. Details of the manufacturing process, control of materials, critical steps, process controls, and process validation are provided in Mallinckrodt’s DMF# ——This DMF has been reviewed by this reviewer and found to be adequate to support the NDA.
The proposed MNTX drug substance specification includes

Real-time stability data (7 batches) ranged from 12 months to 36 months and six months accelerated data (6 batches) were provided at the nominal MNTX batch size that is representative of the commercial process. Real-time and accelerated stability data are also available for up to nine months for three batches for the nominal 65 kg commercial process. All stability studies have been performed by Mallinckrodt using the proposed commercial container closure systems for all batch sizes. Stability data showed no significant changes.

The stability data support the proposed retest date of months for the bulk drug substance stored either inside an , at controlled room temperature, 25°C/60% RH.

B. Description of How the Drug Product is Intended to be Used

The drug product is administered as a subcutaneous injection, no more frequently than one dose in a 24 hour period.

The recommended dose of Relistor Injection, 20 mg/mL, is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg.

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Injection Volume</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pounds</td>
<td>Kilograms</td>
<td></td>
</tr>
<tr>
<td>84 to less than 136</td>
<td>38 to less than 62</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>136 to 251</td>
<td>62 to 114</td>
<td>0.6 mL</td>
</tr>
</tbody>
</table>

In patients with severe renal impairment (creatinine clearance less than 30 ml/min), reduce the dose of Relistor Injection by one-half.

The drug product is to be stored at controlled room temperature 20-25°C (68-77°F). When stored under the specified conditions, an expiration dating period of 24 months can be expected.
Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to ensure the drug product’s identity, strength, quality, purity, potency, and stability as a subcutaneous product for its intended use. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance. At the completion of this review, labeling review among all disciplines has not taken place. Therefore, from a CMC standpoint, this new drug application may be approved pending resolution of minor labeling issue.

III. Administrative

A. Reviewer’s Signature:  
electronically signed in DFS

B. Endorsement Block:  
electronically signed in DFS

C. CC Block:  
entered electronically in DFS
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Jane Chang
2/4/2008 04:48:21 PM
CHEMIST

Moo-Jhong Rhee
2/4/2008 04:56:42 PM
CHEMIST
Chief, Branch III
A. Summary

Methylnaltrexone Bromide Injection, 20 mg/mL has been developed as a subcutaneous injection product (to be taken no more than once daily) for the treatment of opioid-induced constipation. It is supplied in a clear 3 mL glass, single use vial, with gray rubber stopper and aluminum overseal with flip-off-cap. The target fill volume is 0.6 mL per dose. The recommended dose is on a patient weight basis, as indicated below.

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Injection Volume</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>84 to less than 136</td>
<td>38 to less than 62</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>136 to 251</td>
<td>62 to 114</td>
<td>0.6 mL</td>
</tr>
</tbody>
</table>

For patients whose weight falls outside these ranges, dosing at 0.15 mg/kg is recommended.

Drug Substance

The active component in this product is methyl naltrexone (MNTX), a quaternary salt with bromide counterion.

For complete information regarding the synthesis and characterization of this
new molecular entity, reference is made to Mallinckrodt's Type II DMF # which will need to be reviewed.

Characterization

The specification

Limits for individual identified impurities (related compounds) are set at or lower, in accord with ICH guidance, and for individual unidentified impurities at also in accord with ICH. For however, the proposed limit of exceeds the ICH qualification limit, but the applicant indicates that this limit is acceptable based on qualification in non-clinical studies.

At the pre-NDA meeting dated November 1, 2004, FDA discussed with Progenics that FDA is setting a qualification threshold for Agreement was reached that no more that 250 acceptable as an interim specification, but should eventually be in the present submission, an acceptance criterion of is included in the drug substance specification, with a commit to lower the specification to NMT by May, 2007. At the time of this review no revision of this acceptance criterion has yet been received from the sponsor.

Drug Product

The proposed commercial formulation contains 20 mg/mL methylnaltrexone bromide, edetate calcium disodium (CaEDTA), glycine hydrochloride, and sodium chloride in water for injection:

<table>
<thead>
<tr>
<th>Component</th>
<th>Grade</th>
<th>Quantity/ 0.6 mL</th>
<th>Concentration (mg/mL)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnaltrexone Bromide</td>
<td>In-house Standard</td>
<td>12 mg*</td>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>Sodium Chloride</td>
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</table>

a. Input based on 100% potency. This amount will be adjusted based upon actual assay of the drug substance.

All excipients conform to USP/NF requirements, with the exception of glycine hydrochloride, which will conform to an in-house specification.
It should be noted that no clinical trials were conducted with the commercial formulation proposed above. Clinical trials, including Phase III trials, were conducted with a different formulation, one that contained only saline. Since the saline formulation required refrigeration, the proposed commercial product requires only room temperature storage. According to the applicant, both these components, in combination, are required to stabilize the product. Data comparing the bioequivalence of the commercial formulation with the one used in phase 3 clinical trials have been submitted and will need to be evaluated by the Biopharm reviewer.

The relatively uncomplicated manufacturing process involves

The specification

Product Stability: Up to six months of stability data at 25°C/60%RH, 30°C/75%RH, and 40°C/75%RH are provided for three production-scale batches of the proposed commercial product. Additional data (total of nine months) will be provided during the review period, with a proposal for an 18-month expiry. In view of the very limited data that have been submitted, it is premature to comment on the proposed expiry at the present time.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Environmental assessment: Progenics Pharmaceuticals appropriately requests categorical exclusion from preparing an environmental assessment on the basis that the estimated concentration of methyl naltrexone at the point of entry into the aquatic environment will be below 1 part per billion.

B. Critical issues for review
Since glycine hydrochloride will conform to an in-house specification, the adequacy of the specification needs to be carefully evaluated.

The manufacturing process

The pH acceptance criterion that is part of the specification for the drug product allows a range of for pH. However, data submitted by the applicant indicate that the optimum pH range for product stability is . The appropriateness of the proposed range should be evaluated.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

Moo-Jhong Rhee, PhD
Branch Chief

5/25/2007
Date

5/25/2007
Date
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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5/31/2007 12:56:35 PM  
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