CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-100

ADMINISTRATIVE DOCUMENTS

for September 14, 1998

Application: ANDA 75100/000
Stamp: 28-MAR-1997 Regulatory Due:
Applicant: LEK PHARM
VEROVSKOVA 57, 1526
LJUBLJANA, , SI

Priority:
Action Goal:
Brand Name:
Established Name: BROMOCRIPTINE MESYLATE
Generic Name:
Dosage Form: CAP (CAPSULE)
Strength: 5 MG

Org Code: 600
District Goal: 28-MAY-1998

FDA Contacts:

S. OKEEFE	(HFD-617)	301-827-5848	, Project Manager
S. SHERKEN	(HFD-625)	301-827-5848	, Review Chemist
M. SMELA JR	(HFD-625)	301-827-5848	, Team Leader

Overall Recommendation:

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 14-SEP-1998

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 9613457
LEK LJUBLJANA PHARMACEUTICA
VEROVSKOVA 57, 61107
LJUBLJANA, , SI

DMF No:
AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 14-SEP-1998

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Establishment: 1719991
ROSEMONT PHARMACEUTICAL CO
301 SOUTH CHEROKEE ST
DENVER, CO 80223

DMF No:
AADA No:

Profile: CHG OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 14-SEP-1998

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-100 Applicant LEK Pharmaceutical & Chemical Company d.d.

Drug Bromocriptine Mesylate Capsules USP

Strength 5 mg (base)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐

REVIEWER:

1. Project Manager
   Review Support Br 2

DRAFT RECEIPT Date 11/10/98 Initials DF

FINAL ACTION Date 12/1/98 Initials DF

Application Summary:

Original Rec'd date 3/28/97

Date Acceptable for Filing 3/28/97

Patent Certification (type) II

Date of Office Bio Review 12/5/97

Methods Val. Samples Pending Yes ☐ No ☒

30 Day Clock Start N/A End USP

Commitment rcd. from Firm Yes ☐ No ☐

First Generic Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐

Date of EER Status 11/30/95

Date Patent in effect

Citizens Petition/Legal Case Yes ☐ No ☒

(If YES, attach email from PM to Pet. Coord. notifying of pending approval)

Pediatric Exclusivity Tracking System

Date checked 11/10/98

Nothing Submitted ☒

Written request issued ☐

Study Submitted ☐

Sign off 12/1/98

Comments:

2. Div. Dir./Deputy Dir. Date 11/14 Initials [illegible] Date 11/24 Initials

Chemistry Div. I or II

Comments: Satisfactory overall completion CCP

3. Office Level Chem Review (1st Generic Only) Date Initials Date 12/8/98 Initials

Chemistry Div. I or II

Comments: N/A Audit previously performed on Lek's tablet dosage form.

4. Pat Beers Block Date Initials Date Initials

Supv., Review Support Branch

Comments:

Not reviewed; see Rx's review

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11/25/98

REVIEWER:	DRAFT RECEIPT	FINAL ACTION
5. Peter Rickman	Date 12/2/98	Date 12/4/98
Supv., Reg. Support Branch	Initials	Initials
Contains certification Yes ☒ No ☐	Determ. of involvement? Yes ☐ No ☒	
(required by the GDEA if sub after 6/1/92)	Pediatric Exclusivity Tracking System	
Paragraph 4 Certification Yes ☐ No ☒ PII	Date Checked N/A 14,800 patents	
NDA 17-962 002	Nothing Submitted ☑ or exclusivity	
No patent or exclusivity issues	Written request issued ☐	
ESE accepted 11/13/98 for ESES	Study Submitted ☐	
Office Level BIO acceptable 12/1/98		
Comments: 1ST Generic for Capsule - 1ST Generic review done on tablets o'k'd by Dir. Director		
No CP on this product		
6. Jerry Phillips	Date 12/8/98	Date 12/14/98 /S/
Dir. Div. Labeling & Prog. Support	Initials	Initials
Comments: Acceptable GES dated 11/30/98. No D.A.I. effects noted. Bioequivalence study (fed) found acceptable 12/3/98. Office-level bio endorsed 12/1/98. Cover. FPL Acceptable 12/4/98 CMC Acceptable 11/18/98 Methods validation waived. No Citizens Petitions or controlled correspondence currently pending. No patents or exclusivities currently listed. Recommend: Approval Firm permitted to conduct fed (nonfasting) bio study - letter in file		
7. Gordon Johnston	Date	Date
Deputy Director, OGD	Initials	Initials
Patent Cert - P, Yes ☐ No ☐	Petition Status	
Pend. Legal Action Yes ☐ No ☐		
Comments:		
Doug Sporn	Date	Date
Dir., OGD	Initials	Initials
Comments: First-Generic capsule dosage form.		
Roger Williams, M.D.	Date	Date 12/14/98
Dep.Dir., CDER	Initials	Initials
First Generic Approval ☐		
PD or Clinical for BE ☐		
Special Scientific or Reg.Issue ☐		
9. Project Manager /S/	Date 12/14/98	Date
Review Support Branch	Initials	Initials

N/A Pediatric Exclusivity Tracking System (check just prior to notification to firm)

Applicant notification:

12:57 Time notified of approval by phone 1:15 PM Time approval letter faxed

FDA Notification:

12/14/98 Date e-mail message sent to "OGD approvals" account

12/14/98 Date Approval letter copied to "//cder/drugapp" directory

ANDA Number: 75-100

FIRM: Lek Pharmaceutical and Chemical Co.

DOSAGE FORM: Bromocriptine Mesylate Capsules USP.

STRENGTH 5 mg as Bromocryptine base.

CGMP STATEMENT/EER UPDATE STATEMENT:

EER pending.

BIO STUDY: Bio completed its review on 12/5/97. Found acceptable to Parlodel 5 mg, manufactured by Sandoz.

METHODS VALIDATION: - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

N/A. Official methods are USP.

STABILITY:- ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION

Lots 1910596 (Bio batch) and 1930596 (Stability batch) stability data in 30 count c/c system and 100 count c/c systems for 3 months at 40°C/75% RH and for 24 months at 25°C/60% RH were satisfactory.

The containers used for the stability samples are identical to the containers that were described in the Container Section.

LABELING: Found adequate on 11/4/98.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.)

Bio batch 1910596 = capsules. Lek manufactures its own lots of Bromocriptine Mesylate. The manufacturing process is found in The batches passed all USP and in-house tests. It is adequate. Lot 19105696 passed all required tests and specifications in USP & In-house. Lek manufactured the bio batch and used it to qualify Rosemont as their principal packaging site.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Stability batch 1930596 = apsules. Lek manufactured this lot to Qualify Lek as a alternative Packaging site. Lot 1930596 was manufactured by same procedure that was used for the bio batch. It passed all required tests and specifications in the USP & In-house.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Size of proposed production batches = capsules.
Manufacturing process is the same as were the Bio/Stability Batches.

Stephen Sherken 11/17/98

Prepared by Stephen Sherken on 11/5/98. /S/

11/18/98

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **ANDA 75100/000**
Stamp: **28-MAR-1997** Regulatory Due:
Applicant: **LEK PHARM**
VEROVSKOVA 57, 1526
LJUBLJANA, , SI

Priority:
Org Code: **600**
Action Goal:
District Goal: **28-MAY-1998**
Brand Name:
Established Name: **BROMOCRIPTINE MESYLATE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **5 MG**

FDA Contacts: **ID = 122344** , **Project Manager**
S. SHERKEN (HFD-625) 301-827-5848 , **Review Chemist**
M. SMELA JR (HFD-625) 301-827-5848 , **Team Leader**

Overall Recommendation:

ACCEPTABLE on 30-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-SEP-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9613457**
LEK LJUBLJANA PHARMACEUTIC
VEROVSKOVA 57, 61107
LJUBLJANA, , SI

DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-SEP-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Establishment: **1719991**
ROSEMONT PHARMACEUTICAL C
301 SOUTH CHEROKEE ST
DENVER, CO 80223

DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-NOV-1998**
Decision: **ACCEPTABLE**

Responsibilities: **FINISHED DOSAGE PACKAGER**
FINISHED DOSAGE STABILITY TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-100** Date of Submission: **April 9, 1998**

Applicant's Name: **Lek Pharmaceutical and Chemical Co. d.d.**

Established Name: **Bromocriptine Mesylate Capsules, USP 5 mg**

Labeling Deficiencies:

1. CONTAINER (30s and 100s)

   Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. INSERT

   a. The innovator provides a combined insert for the tablets and capsules. We note your application for the tablets (ANDA 74-631) was approved on January 13, 1998. Please revise your insert accordingly.

   b. INDICATIONS AND USAGE

      Revise to read "Bromocriptine mesylate capsules or tablets are indicated..." in the first sentence of each subsection.

   c. PRECAUTIONS

      i. Hyperprolactinemic States - Revise to read "Bromocriptine mesylate capsules or tablets are indicated..." in the sixth sentence.

      ii. Pregnancy - Revise the subsection heading to read as follows:

Pregnancy; Teratogenic Effects, Pregnancy Category B

iii. Nursing Mothers - Do not italicize "used during lactation in postpartum women".

iv. Pediatric Use - Revise to read:

...patients under the age of 15 have...

d. HOW SUPPLIED

Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

Please revise your insert labeling, as instructed above, and submit final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

for November 06, 1998

Application: **ANDA 75100/000**
Stamp: **28-MAR-1997** Regulatory Due:
Applicant: **LEK PHARM**
VEROVSKOVA 57, 1526
LJUBLJANA, , SI

Priority:
Org Code: **600**
Action Goal:
District Goal: **28-MAY-1998**
Brand Name:
Established Name: **BROMOCRIPTINE MESYLATE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **5 MG**

FDA Contacts:

S. OKEEFE	**(HFD-617)**	**301-827-5848**	**, Project Manager**
S. SHERKEN	**(HFD-625)**	**301-827-5848**	**, Review Chemist**
M. SMELA JR	**(HFD-625)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

Establishment: **9610464**
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-SEP-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9613457**
LEK LJUBLJANA PHARMACEUTICA
VEROVSKOVA 57, 61107
LJUBLJANA, , SI
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-SEP-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Establishment: **1719991**
ROSEMONT PHARMACEUTICAL CO
301 SOUTH CHEROKEE ST
DENVER, CO 80223
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO DO**
Milestone Date: **08-SEP-1998**

Responsibilities: **FINISHED DOSAGE PACKAGER**
FINISHED DOSAGE STABILITY TESTER

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-100** Date of Submission: **October 20, 1998**

Applicant's Name: **Lek Pharmaceutical and Chemical Co. d.d.**

Established Name: **Bromocriptine Mesylate Capsules, USP 5 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: April 9, 1998 (30s and 100s). See comment regarding Rx only.

Professional Package Insert Labeling: October 20, 1998

Revisions needed post-approval:
INSERT

a. TITLE

   i. Increase the prominence of the established name and expression of strength.

   ii. We encourage the inclusion of "℞ only" in this section.

b. PRECAUTIONS

   i. Pregnancy - Revise the subsection heading to read as follows:

      Pregnancy: Teratogenic Effects, Pregnancy Category B

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Parlodel® Capsules

NDA Number: 17-962

NDA Drug Name: Parlodel® Capsules

NDA Firm: Sandoz Pharmaceutical Corp.

Date of Approval of NDA Insert and supplement #:
17-962/S-052 - April 2, 1998

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the jacket for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the FF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. Firm has CRC cap on both sizes.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Parlodel®; Approved April 2, 1998; Revised November 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store below 77°F (25°C). Dispense in a tight, light-resistant container.

   ANDA: Store below ~~25°C (77°F)~~. Dispense in a tight, light-resistant container.

   USP: Preserve in a tight, light-resistant containers.

4. Product Line:

   The innovator markets their product in bottles of 30s and 100s.

   The applicant proposes to market their product in bottles of 30s and 100s.

5. The capsule imprints have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 2051, Vol. 1.6.

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1328 and 29, Vol. 1.4.

8. All manufacturing will be performed by Lek. Rosemont Pharmaceutical Corporation packages the product. See pages 1424,29 and 30 in Vol. 1.4.

9. Container/Closure:

   This product will be packaged in amber glass bottles with CRC caps. See page 1729, Vol. 1.5.

10. This application is for the 5 mg capsules. The firm has submitted another ANDA for the 2.5 mg tablet. The innovator has a combined insert and in the DOSAGE AND ADMINISTRATION section of the labeling it states "tablets" throughout. We requested the firm combine the inserts or replace "tablets" with it's corresponding "mg" amount. The 2.5 mg tablet was approved in January 1998.

Date of Review: November 3, 1998

Date of Submission: October 20, 1998

Reviewer: /S/ **Date:** 11/3/98

Team Leader: **Date:**

/S/ 11/4/98

4/4/99

cc: /S/

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-100** Date of Submission: **April 9, 1998**

Applicant's Name: **Lek Pharmaceutical and Chemical Co. d.d.**

Established Name: **Bromocriptine Mesylate Capsules, USP 5 mg**

Labeling Deficiencies:

1. CONTAINER (30s and 100s)

   Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. INSERT

   a. The innovator provides a combined insert for the tablets and capsules. We note your application for the tablets (ANDA 74-631) was approved on January 13, 1998. Please revise your insert accordingly.

   b. INDICATIONS AND USAGE

      Revise to read "Bromocriptine mesylate capsules or tablets are indicated..." in the first sentence of each subsection.

   c. PRECAUTIONS

      i. Hyperprolactinemic States - Revise to read "Bromocriptine mesylate capsules or tablets are indicated..." in the sixth sentence.

      ii. Pregnancy - Revise the subsection heading to read as follows:

Pregnancy: Teratogenic Effects, Pregnancy Category B

iii. Nursing Mothers - Do not italicize "used during lactation in postpartum women".

iv. Pediatric Use - Revise to read:

...patients under the age of 15 have...

d. HOW SUPPLIED

Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "℞ only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

Please revise your insert labeling, as instructed above, and submit final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: April 9, 1998 (30s and 100s). See comment regarding Rx only.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Parlodel® Capsules

NDA Number: 17-962

NDA Drug Name: Parlodel® Capsules

NDA Firm: Sandoz Pharmaceutical Corp.

Date of Approval of NDA Insert and supplement #:
17-962/S-052 - April 2, 1998
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the jacket for side-by-side review.

Basis of Approval for the Carton Labeling: Labeling in file folder and labels submitted in the jacket for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the FP?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. Firm has CRC cap on both sizes.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Parlodel®; Approved April 2, 1998; Revised November 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store below 77°F (25°C). Dispense in a tight, light-resistant container.

   ANDA: Store below 25°C (77°F). Dispense in a tight, light-resistant container.

   USP: Preserve in a tight, light-resistant containers.

4. Product Line:

   The innovator markets their product in bottles of 30s and 100s.

   The applicant proposes to market their product in bottles of 30s and 100s.

5. The capsule imprints have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 2051, Vol. 1.6.

6. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 1328 and 29, Vol. 1.4.

8. All manufacturing will be performed by Lek. Rosemont Pharmaceutical Corporation packages the product. See pages 1424,29 and 30 in Vol. 1.4.

9. Container/Closure:

   This product will be packaged in amber glass bottles with CRC caps. See page 1729, Vol. 1.5.

10. This application is for the 5 mg capsules. The firm has submitted another ANDA for the 2.5 mg tablet. The innovator has a combined insert and in the DOSAGE AND ADMINISTRATION section of the labeling it states "tablets" throughout. We requested the firm combine the inserts or replace "tablets" with it's corresponding "mg" amount. The 2.5 mg tablet was approved in January 1998.

Date of Review: April 21, 1998

Date of Submission: April 9, 1998

Reviewer: C. Holquist **Date:** 5/22/98

Team Leader: /S/ **Date:** 5/21/98

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cc:

2.L

M E M O R A N D U M

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

DATE: May 21, 1997

FROM: Anna Marie H. Weikel
Consumer Safety Officer
HFD-615

SUBJECT: Refuse to File Letter for ANDA 75-100

I double-checked the original submission and found the dissolution data on pp. 721-731, as cited in the May 15, 1997, letter. However, I also noted that this item was not included in the original table of contents which would be a requirement for our cursory administrative review.

Because the data was located in the original submission, although, not identified in the table of contents; Peter Rickman agreed that an exception should be made and the firm should be given the original filing date this one time only.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-100 Date of Submission: March 25, 1997

Applicant's Name: Lek Pharmaceutical and Chemical Co. d.d.

Established Name: Bromocriptine Mesylate Capsules, USP 5 mg

Labeling Deficiencies:

1. CONTAINER (30s and 100s)

   a. Revise the strength to read as follows:

      Bromocriptine Mesylate Capsules, USP

      5 mg*

   b. Revise the "Each capsule contains..." statement to read as follows:

      *Each capsule contains bromocriptine mesylate equivalent to 5 mg bromocriptine.

2. INSERT

   a. DESCRIPTION

      i. Revise paragraph one to read as follows:

         ...activity. Bromocriptine mesylate is chemically designated as...(salt).* Bromocriptine mesylate is a white or slightly colored, fine crystalline powder odorless or having a weak characteristic odor.

      ii. Revise the listing of ingredients to read as follows:

         Each capsule for oral administration contains bromocriptine mesylate equivalent to 5 mg bromocriptine. In addition, each capsule contains the following inactive ingredients:...

b. ADVERSE REACTIONS

i. Hyperprolactinemic Indications, paragraph two - ...to 1.25 mg two...

ii. Adverse Events Observed in Other Conditions: Postpartum Patients - Delete the bold and underline from line 10.

c. DOSAGE AND ADMINISTRATION

We encourage you to combine this package insert with your application for bromocriptine mesylate tablets, USP 2.5 mg (ANDA 74-631) or delete reference to the "tablet" and replace with the corresponding "mg" amount.

d. HOW SUPPLIED

We encourage the inclusion of your NDC numbers.

Please revise your insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-100 Date of Submission: March 25, 1997

Applicant's Name: Lek Pharmaceutical and Chemical Co. d.d.

Established Name: Bromocriptine Mesylate Capsules, USP 5 mg

Labeling Deficiencies:

1. CONTAINER (30s and 100s)

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      5 mg*

   b. Revise the "Each capsule contains..." statement to read as follows:

      *Each capsule contains bromocriptine mesylate equivalent to 5 mg bromocriptine.

2. INSERT

   a. DESCRIPTION

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To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Parlodel® Capsules

NDA Number: 17-962

NDA Drug Name: Parlodel® Capsules

NDA Firm: Sandoz Pharmaceutical Corp.

Date of Approval of NDA Insert and supplement #: 17-962/S-051
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Labels in file folder and labels submitted in the jacket for side-by-side review.
Basis of Approval for the Carton Labeling: Labeling in file folder and labels submitted in the jacket for side-by-side review.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. Firm has CRC cap on both sizes.	X		
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
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Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
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Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
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Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Parlodel®; Approved July 3, 1996; Revised February 1996).

2. Patent/ Exclusivities:

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6. Inactive Ingredients:

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ADMINISTRATION section of the labeling it states "tablets" throughout. We have requested the firm combine the inserts or replace "tablets" with it's corresponding "mg" amount.

Date of Review: September 19, 1997

Date of Submission: March 25, 1997

Reviewer: C. Halquist Date: 9/22/97

Team Leader: /S/ Date: 9/23/97

cc:

Application: **ANDA 75100/000**
Stamp: **28-MAR-1997** Regulatory Due:
Applicant: **LEK PHARM**
VEROVSKOVA 57, 1526
LJUBLJANA, , SI

Priority:
Action Goal:
Brand Name:
Established Name: **BROMOCRIPTINE MESYLATE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **5 MG**
Org Code: **600**
District Goal: **28-MAY-1998**

FDA Contacts: **S. OKEEFE** **(HFD-617)** **301-827-5848 , Project Manager**
M. SMELA JR **(HFD-625)** **301-827-5848 , Team Leader**

Overall Recommendation:

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 18-JUN-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Establishment: **9613457**
LEK LJUBLJANA PHARMACEUTIC
VEROVSKOVA 57, 61107
LJUBLJANA, , SI
DMF No:
AADA No:

Profile: **CHG** OAI Status **NONE**
Last Milestone: **OC RECOMMENDAT 23-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:
DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Establishment: **1719991**
ROSEMONT PHARMACEUTICAL C
301 SOUTH CHEROKEE ST
DENVER, CO 80223
DMF No:
AADA No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO DO 23-MAY-1997**
Responsibilities:
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

CDER Establishment Evaluation Report
for May 22, 1997

Application: **ANDA 75100/000**
Stamp: **28-MAR-1997** Regulatory Due:
Applicant: **LEK PHARM**
VEROVSKOVA 57, 1526
LJUBLJANA, , SI

Priority:
Action Goal:
Brand Name:
Established Name: **BROMOCRIPTINE MESYLATE**
Generic Name:
Dosage Form: **CAP (CAPSULE)**
Strength: **5 MG**

Org Code: **600**
District Goal: **28-MAY-1998**

FDA Contacts: **S. OKEEFE (HFD-617) 301-827-5848 , Project Manager**
M. SMELA JR (HFD-625) 301-827-5848 , Team Leader

Overall Recommendation:

Establishment: **9613457**
LEK LJUBLJANA PHARMACEUTICA
VEROVSKOVA 57, 61107
LJUBLJANA, , SI

DMF No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC** **22-MAY-1997**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC** **22-MAY-1997**

Establishment: **1719991**
ROSEMONT PHARMACEUTICAL CO
301 SOUTH CHEROKEE ST
DENVER, CO 80223

DMF No:

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC** **22-MAY-1997**

Responsibilities:
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

ANDA/AADA PROCESSING RECORD

ANDA/AADA NO. 75,100

DATE		INITIALS
3/28/97	Date received by Document Room	meB
3/31/97	Date received by Program Support Staff	meB
4/4/97	Date forwarded to CSO/CSO Tech. for review	meB
———	Date filling review completed/forwarded for supervisory review	———
5/4/97	Date sent to typing	AMW
———	Date typing completed	———
———	Date sent for Director's signature	———
———	Date of OGD signature	———

74631 capsules 2.5 mg

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

AADA / ANDA # 75-102 FIRM NAME Lek

DRUG NAME: Bromocriptine mesylate

DOSAGE FORM: capsules USP 5mg

Supervisory Chemist (___) Labeling Reviewer (Carol Holquist CA2)

Random Assignment (Random II)

	YES	NO
Comments ECI ✓ On Cards ✓		
Therapeutic Code 3030900 ✓ D opamine agents	3/25/97 3/28/97	
Methods Validation Package (3 copies) (NO) Required for Non-USP drugs		
Cover Letter	✓	
Letter of Authorization	✓	
U.S. Agent (If needed, Countersignature on 356h)	✓	
DMF Referral(s) Q. 1338	✓	
356 Form - Completed /Original Signature	✓	
Table of Contents	✓	
Listed Drug/Firm Parlodel Sandoz	✓	
AADA Monograph	na	
Information to show proposed product is the same as the listed product: (i) (a) indications (ii) active ingredients(s) iii (a) route (b) dosage form (c) strength (iv) labeling -- side by side comparison - insert:	✓	
Container:	✓	
Same Formulation?	na	
Ophthalmics/Otics/Externals Parenterals		
Parenteral: Same Size Container / (strength/volume)		
Petition Required		✓
Debarment Certification ✓	✓	
List of Convictions		
Third Copy Certification ✓ ✓	✓	
Patent Certification ✓	✓ 2	
Use Patent Statement / Exclude Use in labeling / indications?		✓
Exclusivity Addressed	✓	

Five year exclusivity? If yes, cannot be filed until expiration of exclusivity or after 4 years if patent challenged.		✓
Labeling: 4 copies of draft (✓) or 12 copies of FPL ( )	✓	
Statement re Rx/OTC Status	✓	
Components & Composition (Unit Composition) p 1447	✓	
Specifications and Tests for Active Ingredients and Dosage Form		
Source of Active Ingredient(s)	✓	
COA from Manufacturer of Active Ingredient(s)	✓	
Applicant COA	✓	
COA for finished product p. 1851	✓	
Specifications and Tests for Inactive Ingredients		
Source of Inactive Ingredients Identified	✓	
Applicant COA for Inactive Ingredient	✓	
COA from Manufacturer of Inactive Ingredients	✓	
Manufacturing Controls	✓	
Batch Formulation 200,000 capsules	✓	
Master Production Batch Record for largest batch size intended for production (No more than 10x pilot batch)	✓	
Certification of GMP	✓	
Description of Facilities	✓	
Address of Manufacturing Site for Production Batches	✓	
Manufacturing Procedures (Batch Records)	✓	
Package entire test batch	✓	
Batch Number(s) 1910596 & 1930596	✓	
Mfg. Facility _____	✓	
If Sterile product: Aseptic Fill _____ Terminal Sterilization _____	na	
Stability Profile Including stability Data (Use of Stability Indication Method)		
3 months Accelerated Stability Data p. 2081 + 2124	✓	
Batch Number(s) Listed on Stability Records (Batch number(s) the same as the test batch	✓	
Sample Statement Plus Data	✓	
Bioavailability/Bioequivalence Study	✓	
In Vivo Study/Waiver Request		
Comparative Dissolution Data		✓

Paragraph IV bio study acceptable for filing		
Date acceptable for filing		
Computer Disk Submitted		
Environmental Impact Analysis	✓	
Compliance Statement	na	

Reviewing CSO / CST (/S/

Date _____

Recommendation: FILE **REFUSE to FILE**

Supervisory Concurrence / Date _____

Duplicate copy sent to Bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD _____ **for Consult**

Type of Consult:

Micro Assignment: