

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-553

ADMINISTRATIVE DOCUMENTS

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 : December 4, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) *Davis 12/4/03*

SUBJECT: Examination of the request for bioequivalence study submitted with an ANDA for Medroxyprogesterone Acetate Injectable Suspension USP, 150 mg/mL, 1 mL Vial determine if the application is substantially complete for filing.

Gensia Sicor Pharmaceuticals, Inc. submitted ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension USP, 150 mg/mL, 1 mL Vial. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for bioequivalence study submitted by Gensia Sicor on November 27, 2002 for its Medroxyprogesterone Acetate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76-553 FIRM NAME Gensia Sicon Pharmaceuticals Inc.

DRUG NAME Medroxy progesterone Acetate, USP, 150 mg/mL

DOSAGE FORM Injectable Suspension

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

- Study meets statutory requirements
 Study does NOT meet statutory requirements
Reason: _____
- Waiver meets statutory requirements
 Waiver does NOT meet statutory requirements
Reason: _____

RECOMMENDATION: COMPLETE INCOMPLETE

Reviewed by:

Mamali Gokhal

Date: 12/13/02

Reviewer

Gurjapal Singh

Date: 12-16-02

Team Leader

Rah P. Kumar

Date: 12/16/02

Director, Division of Bioequivalence

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	✓				
Assay Methodology	✓				
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data		✓			N/A
Pre-screening of Patients	✓				
Chromatograms	✓				
Consent Forms	✓				
Composition	✓				
Summary of Study	✓				
Individual Data & Graphs, Linear & Ln	✓				
PK/PD Data Disk (or Elec Subm)	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				
Clinical Site	✓				
Analytical Site	✓				
Study Investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				

BIO Batch Size	✓				
Assay of Active Content Drug	✓				CMC Vol. 1.2
Content Uniformity	✓				CMC CMC Vol. 1.2
Date of Manufacture	✓				CMC Vol. 1.2
Exp. Date of RLD	✓				
BioStudy Lot Numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data		✓			N/A

Additional Comments regarding the ANDA:

**APPEARS THIS WAY
ON ORIGINAL**

RECORD OF TELEPHONE CONVERSATION

<p>Sicor was contacted to provide a telephone amendment for the following:</p> <p>1. Copy of the dissolution method and validation report.</p> <p>2. Updated release and stability specifications to include dissolution limits as recommended by DBE: 15 min NMT — % 60 min — % 2880 min (48 hr) NLT — %</p> <p>3. Retest of retained 3 month accelerated stability samples against the dissolution limits recommended by DBE.</p> <p>Sicor will provide the requested amendment within 10 days.</p>	<p>Date 5/11/04</p>
	<p>ANDA NUMBER</p> <p>76-552 and 76-553</p>
	<p>IND NUMBER</p>
	<p align="center">TELECON</p>
	<p>INITIATED BY</p> <p>SPONSOR</p> <p>FDA X</p>
	<p>PRODUCT NAME</p> <p>Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL</p>
	<p>FIRM NAME</p> <p>Sicor Pharmaceuticals</p>
	<p>NAME OF PERSON WITH WHOM CONVERSATION WAS HELD</p> <p>Elvia Gustavson</p>
	<p>TELEPHONE NUMBER</p> <p>949-455-4724</p>
	<p>SIGNATURE</p> <p>P. Chen</p> <p><i>P. Chen 5/11/04</i></p>

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CC: ANDA

Chem Div I, T-con Notebook

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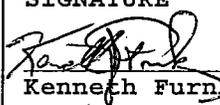
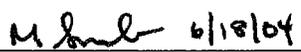
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information from

RECORD OF TELEPHONE CONVERSATIONS
DATED 5/24/2004 AND 5/26/2004

RECORD OF TELEPHONE CONVERSATION

<p>Sicor was contacted regarding the established related substances specifications for the Medroxyprogesterone Acetate Injectable Suspension drug products (vial; 76-553 and syringe; 76-552).</p> <p>Sicor was asked to revise their related substances specifications for the drug product as a result of further consideration within the Division (originally, we accepted D.P. specifications equivalent to the USP D.S. specifications).</p> <p>We spoke with Sonja Hernandez in Elvia Gustafson's absence.</p> <p>We informed her that Sicor should establish specifications for the drug product equivalent to those established for the drug substance (—% for the identified related substances in Medroxyprogesterone Acetate) unless the specific related compound is shown to change over time, with an exception for D.P. unknowns, which we would allow up to —% (D.S. unknown limit is —%). Limits for those that increase would be based on stability data. We noted that the actual levels reported for the drug substance and drug products through shelflife do not appear to be close to the current limits.</p> <p>Sonja indicated that she understood what we were asking, and would submit a response as a telephone amendment to both applications with a FAX copy to Mr. Furnkranz.</p> <p>We also discussed the issue regarding the dissolution data for ANDA #76-552 (we requested that Sicor provide dissolution data utilizing the new method at the — month test station in order to support a — month expiration date for the drug product). However, Sicor indicated that that test point will not be until 8/15/04). We indicated that we could not hold the application open til then, and would need to issue a letter. Sonja indicated that she will prepare a response to each application separately, and will address the dissolution issue as well as the related substances specifications in the amendment to ANDA #76-552. Sicor will provide the requested telephone amendments within 10 days.</p>	Date 6/18/04
	<p>ANDA NUMBER</p> <p>76-552 and 76-553</p>
	<p>IND NUMBER</p>
	<p>TELECON</p>
	<p>INITIATED BY</p> <p>SPONSOR</p> <p>FDA X</p>
	<p>PRODUCT NAME</p> <p>Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL</p>
	<p>FIRM NAME</p> <p>Sicor Pharmaceuticals</p>
	<p>NAME OF PERSON WITH WHOM CONVERSATION WAS HELD</p> <p>Sonja Hernandez for Elvia Gustafson</p>
	<p>TELEPHONE NUMBER</p> <p>949-455-4724</p>
	<p>SIGNATURE</p> <p> 6/18/04 Kenneth Furnkranz</p> <p> 6/18/04 Mike Smela</p>

V:\FIRMSNZ\SICOR\TELECONS\76552.tc.18June2004.doc

CC: ANDA

Chem Div I, T-con Notebook

RECORD OF TELEPHONE CONVERSATION

Office of Generic Drugs
Division of Chemistry 1
Team 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:6/18/04
NAME/TITLE OF INDIVIDUAL(S):Rosalie Lowe
FIRM:Sicor
PRODUCT NAME: MPA Injectable Suspension
TEL #:She called

Notes of Conversation:She called to follow up with the telephone conversation earlier today with Sonja Hernandez and myself and Ken Furnkranz. She said they had no problem with the impurity issue and could amend both the vial (76553) and syringe (76552) ANDAs. She had an issue with the syringe ANDA because it was currently pending a telephone amendment with dissolution data. They have no accelerated samples and the product does not reach — months until late august/early September. Sicor desires — month expiry (not —) even if it means waiting for the approval. I said we would not hold the ANDA open for another 2 months. We agreed to the following:

1. 76553 would be amended separately by telephone amendment to respond to the impurity issue.

2. OGD will issue NA Minor on 76552 addressing both the dissolution issue and the impurity issue. Sicor will respond when the data is available.

SIGNATURE OF OGD REPRESENTATIVES:

M. Smela
6/18/04

Location of Electronic Copy: V:\firmsnz\sicor\telecons\061804

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-553

CORRESPONDENCE

GensiaSicor™
PHARMACEUTICALS
A sicor Company

November 27, 2002

Mr. Gary Buehler
 Office of Generic Drugs
 Center for Drug Evaluation and Research
 Food and Drug Administration
 Metro Park North II, HFD-600
 Attention: Documentation and Control Room 150
 7500 Standish Place
 Rockville, MD 20855-2773

505 (2) (A) OK
 OP-JAN-2003
 [Handwritten Signature]

**RE: Medroxyprogesterone Acetate Injectable
 Suspension, USP, 150 mg/mL
 ANDA: Number to be Assigned**

Dear Mr. Buehler:

In accordance with Section 314.92 of the *Code of Federal Regulations, Title 21*, we hereby submit an Abbreviated New Drug Application for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, a parenteral preparation supplied as:

Strength	Drug Content	How Supplied
150 mg/mL	150 mg per Vial	1 mL fill in a 2 mL Single Dose Vial

Gensia Sicor's proposed drug product is the generic version of Pharmacia & Upjohn's Depo-Provera® (Medroxyprogesterone Acetate Injectable Suspension, USP), pursuant to NDA No. 20-246 (001). Pharmacia & Upjohn's drug product appears in the FDA listing titled *Approved Drug Products with Therapeutic Equivalence Evaluation, 22nd Edition*. The approved drug product marketed by Pharmacia & Upjohn is available in 150 mg/1 mL single dose vials.

Our proposed drug product, Medroxyprogesterone Acetate Injectable Suspension, USP, has the same active and inactive ingredients, dosage form, strength, route of administration, and conditions of use as Pharmacia & Upjohn's listed drug product.

Medroxyprogesterone Acetate Injectable Suspension, USP, will be packaged in clear glass vials. The vials will be sealed with stoppers from _____ composed of _____ Gray.

RECEIVED

NOV 29 2002

OGD / CDER

Mr. Gary Buehler
November 27, 2002
Page 2

One (1) stability lot of the drug product was manufactured and data is presented in **Section XVII** of this application.

Four (4) copies of the proposed labeling have also been provided in **Section V** of the application in both the archival and review copies.

The application consists of sixteen (16) volumes and has been formatted in accordance with the Office of Generic Drug's Guidance for Industry, Organization of an ANDA, OGD #1, issued February 1999. Copies are provided as follows:

- 1) One (1) Archival Copy bound in Blue Jackets
- 2) One (1) Review Copy bound in Red Jackets (bioequivalence portion bound in Orange Jackets)

A true copy of this application, which was bound in Burgundy Jackets, has been submitted to the U.S. Food and Drug Administration, Los Angeles District Office.

Since the stability indicating methods are non-compendial, three (3) additional methods validation packages have been included in this application and are marked "Analytical Methods". These three additional copies are identical to **Section XVI** as presented in the archival and review copies, and have been separately bound in Black Jackets.

The complete clinical report (including case report forms), SAS data sets, and supplemental report are provided in **Volumes 4-16** for the *In Vivo* bioequivalence study for Gensia Sicor's Medroxyprogesterone Acetate Injectable Suspension, USP. The review copy of the bioequivalence portion includes **Sections I-VII** of the ANDA and is separately bound in Orange Jackets.

The bioequivalence data is presented in electronic format to provide an accurate and complete copy of the data suitable for inspection, review, and copying in accordance with the Guidance for Industry, "Providing Regulatory Submissions in Electronic Format-General Considerations", issued January 1999. The data is provided on one (1) diskette in Version 5 SAS Transport Format in **Volume 4** of this application and has been formatted in accordance with Guidance for Industry, "Providing Regulatory Submissions in Electronic Format-ANDAs", issued June 2002. The diskette contains SAS data sets for both the original report and the analyses in the supplement to the report.

Mr. Gary Buehler
November 27, 2002
Page 3

We trust you will find the information in this application satisfactory for your review and approval. If there are any questions concerning this application, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Elvia O. Gustavson
Director, Regulatory Affairs

cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612



January 2, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

NC

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to the telephone conversation between Gensia Sicor and Ms. AriaAnne Camphrie of January 2, 2003, where Ms. Camphrie requested that Gensia Sicor submit the actual FDA Form 3454.

In accordance with the provisions of Section 314.96(a)(3) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the actual FDA Form 3454. The document immediately follows.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse
District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

RECEIVED

JAN 06 2003

OGD / CDER

ANDA 76-553

Gensia Sicor Pharmaceuticals, Inc.
Attention: Elvia Gustavson
19 Hughes
Irvine, CA 92618-1902

JAN -6 2003

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated January 2, 2003 and your correspondence dated January 2, 2003.

NAME OF DRUG: Medroxyprogesterone Acetate Injectable Suspension
USP, 150 mg/mL, 1 mL vials

DATE OF APPLICATION: November 27, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 29, 2002

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-553

cc: DUP/Jacket

Division File

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-92

HFD-615/M.Bennett

HFD-600/

Endorsement:

HFD-615/GDavis, Chief, RSB *Davis* 06-JAN-2003 date

HFD-615/ACamphire, CSO *Frienne Camphire* date 01/03/03

Word File

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F/T EEH 01/03/03

ANDA Acknowledgment Letter!

April 25, 2003

ORIG AMENDMENT

N/A

FPL

Mr. Gary Buehler
Office of Generic Drugs
CDER/FDA
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL (vial)
ANDA No. 76-553**

LABELING AMENDMENT

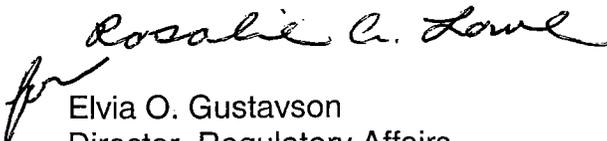
Dear Mr. Buehler:

Reference is made to Gensia Sicor's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to the Agency's facsimile dated March 24, 2003.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **labeling** information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,


Elvia O. Gustavson
Director, Regulatory Affairs

S:\Medroxyprogesterone76553-vial\Amends\Amend 2 labeling.doc

cc: Mr. Alonza Cruse, District Director
FDA/LA District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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APR 28 2003
OGD / CDER

76-553
21

NAT
JWB
7/28/03

NEW CORRESP
NC

July 2, 2003

Mr. Gary Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Change of Corporate Company Name

GENERAL CORRESPONDENCE

Dear Mr. Buehler:

In accordance with the provisions of Section 314.97 of the *Code of Federal Regulations, Title 21*, we hereby notify FDA that effective July 15, 2003, Gensia Sicor Pharmaceuticals, Inc. intends to change its corporate company name to SICOR Pharmaceuticals, Inc. Please note there is no transfer of corporate assets or ownership due to the name change of the company. This notification represents a change in company name only.

Included with this letter is a listing of all approved, tentatively approved, and pending ANDAs that will convert under the name of SICOR Pharmaceuticals, Inc. For the convenience of the Agency, we are providing 122 copies of this letter such that there are two letters available per ANDA for filing purposes.

We trust that the information provided in this correspondence is satisfactory to effect the change of company name. Should you have any questions regarding this matter, please feel free to contact me at (949) 457-2808 or Ms. Elvia Gustavson, Director, Regulatory Affairs at (949) 455-4724.

Sincerely,



Rosalie A. Lowe
Director, Regulatory Affairs

Attachment

- cc: Ms. Gladys Lee Holley, Technical Information Specialist
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Rockville, MD 20855
- Mr. Alonza Cruse, District Director
U.S. Food and Drug Administration
Los Angeles District
19900 MacArthur Blvd., Suite 300, Irvine, CA 92612

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JUL 07 2003

OGD / CDER

S:\Name Change\2003 Company Name Change FDA ltr.doc

19 Hughes
Irvine, CA 92618
Toll Free: 800.729.9991
Telephone: 949.455.4700
Fax: 949.855.8210
www.sicor.com

July 28, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

MINOR CHEMISTRY AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to the Agency's facsimile dated May 16, 2003.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested.

On July 2, 2003, we notified the Agency that Gensia Sicor Pharmaceuticals, Inc. changed the corporate company name to SICOR Pharmaceuticals, Inc. Please note we make this submission using the new corporate company name, SICOR Pharmaceuticals, Inc. Although we have initiated changes to documents revising the corporate company name to SICOR Pharmaceuticals, Inc, there are still some documents in this submission with the previous company name, Gensia Sicor Pharmaceuticals, Inc.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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JUL 29 2003

OGD/CDEH

*NW
7-28-03*

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information from

FDA FAX 5/16/03 CHEMISTRY DEFICIENCIES



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP status of the firms referenced in the ANDA is currently being evaluated by our Office of Compliance. A satisfactory evaluation is required for approval.
2. Your response should also address the labeling deficiencies.
3. Please provide any additional available long-term stability data.
4. Your sterility assurance information is pending review.
5. Your bioequivalence information is pending review.

Sincerely yours,

Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

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information from

 FDA FAX 10/10/2003 CHEMISTRY DEFICIENCIES

2. Your bioequivalence information is pending review.

Sincerely yours,

M. Smela for

Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

October 16, 2003

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773



**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

MINOR CHEMISTRY AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to our amendment dated July 28, 2003. Further reference is also made to the Agency's facsimile dated October 10, 2003.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Elvia O. Gustavson
Director, Regulatory Affairs

S:\Medroxyprogesterone76553-vial\Amends\Amend4.doc

cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

RECEIVED

OCT 17 2003

OGD/CDEK



36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-553

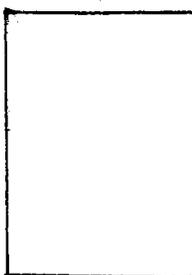
APPLICANT: SICOR Pharmaceuticals, Inc.

DEC - 1 2003

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable Suspension USP,
150 mg/mL, 1 mL vials

The deficiency presented below represents a MINOR deficiency:

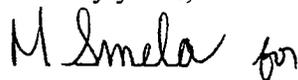
A. Deficiency:



B. In addition to responding to the deficiency presented above, please note and acknowledge the following comments in your response:

1. The CGMP status of the firms referenced in the ANDA is currently being evaluated by our Office of Compliance. A satisfactory evaluation is required for approval.
2. Your bioequivalence information is pending review.
3. Please provide any additional stability data that is available.

Sincerely yours,



Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

19 Hughes
Irvine, CA 92618
Toll Free: 800.729.9991
Telephone: 949.455.4700
Fax: 949.855.8210
www.sicor.com

December 12, 2003

ORIG AMENDMENT
N/A/M

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

MINOR CHEMISTRY AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to our amendment dated October 16, 2003. Further reference is also made to the Agency's facsimile dated December 1, 2003.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie A. Lowe

for
Elvia O. Gustavson
Director, Regulatory Affairs

S:\Medroxyprogesterone76553-vial\Amends\Amend5.doc

cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District
19900 MacArthur Blvd., Suite 300
Irvine, CA 92612

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DEC 15 2003

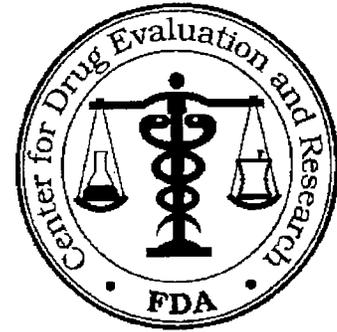
OGD/CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-553

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 04 2004



APPLICANT: SICOR Pharmaceuticals, Inc.

TEL: 949-455-4724

ATTN: Elvia O. Gustavson

FAX: 949-583-7351

FROM: Beth Fabian-Fritsch

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 27, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Medroxyprogesterone Acetate Injectable Suspension USP, 150 mg/mL, 1 mL vials.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 3 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

FEB 04 2005

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-553

APPLICANT: GENSLIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable Suspension, 150 mg/ml.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You stated that subjects # 65 and # 101 were dropped after 83 days and 72 days respectively. Information submitted in the Analytical Report indicated that samples from these subjects were collected and assayed (See Analytical Report: 124 subjects x 39 samples/subject=4846 samples minus 33 undelivered samples = 4803). Since samples were collected long enough to properly characterize the absorption phase of the drug and were already assayed, please include plasma data from these subjects in the statistical analysis of AUC_t , AUC_i and C_{max} .
2. You reported that K_{el} cannot be determined for 12 subjects. However, it appears that it is possible to estimate K_{el} for 8 of these subjects. Please determine K_{el} and AUC_i for the following subjects as follows:

<u>Subject #</u>	<u>Start time</u> (hrs)	<u>Stop time</u> (hrs)
8	1320	2664
11	1656	2856
18	1488	2856
20	1824	2856
30	1320	2856
41	1824	2856
76	984	2856
79	1320	2856

Please re-run the ANOVA and calculate 90% C.I. on AUC_i for all subjects.

3. The following comments pertain to reassays of plasma samples in the bioequivalence study
 - a. Please include criteria for selection of samples for the reassay for confirmation of the first analysis in your Standard Operating Procedures

(SOPs). The SOP should include procedures for the determination of which samples are to be reassayed and acceptance criteria for handling reassay values. The data should be analyzed using both original as well as reassay values. Without objective criteria established prior to the beginning of the study, these reassay values will not be accepted.

- b. Based on the irregularities observed in the plasma concentration-time profiles, please provide justification for not selecting the following subjects for confirmation of the first analysis: Subject # 8, 41, 54, 82, 83, 85, 99, 100 and 124.
 - c. Please provide a theoretical/statistical basis for using $2\sqrt{2}CV$ as an acceptance criterion for confirmation of the first measurement in your repeat assays.
4. The SOP for reassays due to values higher than the upper limit of quantitation and the reassays due to poor chromatography should be provided, along with criteria for selection of reported values. Please submit a table of original values and reported values for review.
 5. Please include a table with explanations for all missing samples.
 6. Please provide long term stability data. Long term stability should exceed the time of first sample collection and the time of the last sample analysis.
 7. Please provide content uniformity/potency of the test and reference products.
 8. Please develop a dissolution method for your product. The following CDER guidance can be used as a guide in developing a dissolution methodology and setting specifications: "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In-Vivo/In-Vitro Correlations".

9. Please provide a table of AUCt/AUCi ratios mean and range for all subjects.

Sincerely yours,

for 

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

19 Hughes
Irvine, CA 92618
Toll Free: 800.729.9991
Telephone: 949.455.4700
Fax: 949.855.8210
www.sicor.com

February 20, 2004

Mr. Gary Buehler
OGD/CDER
Food and Drug Administration
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A/B

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

**BIOEQUIVALENCY AMENDMENT
EXPEDITED REVIEW REQUESTED**

Dear Mr. Buehler:

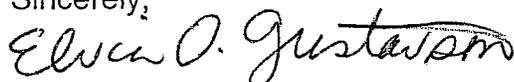
Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to the Agency's facsimile dated February 4, 2004.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide additional **bioequivalency** information requested.

Given the fact that this is a first generic, we hereby request the Division of Bioequivalency to expedite the review of this amendment.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District

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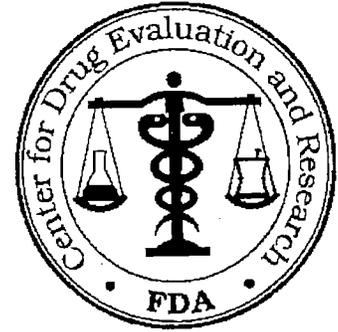
FEB 23 2004

OGD/CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-552 and 76-553

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



MAR 30 2004

APPLICANT: SICOR Pharmaceuticals, Inc.

TEL: 949-455-4724

ATTN: Elvia O. Gustavson

FAX: 949-583-7351

FROM: Beth Fabian-Fritsch *BFF*

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on November 27, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Medroxyprogesterone Acetate Injectable Suspension USP, 150 mg/mL (Prefilled Syringe) and Medroxyprogesterone Acetate Injectable Suspension USP, 150 mg/mL, 1 mL vials.

Reference is also made to your amendment(s) dated: February 20, 2004 and February 23, 2004.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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MAR 30 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-552 & 76-553

APPLICANT: GENSLIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable
Suspension, 150 mg/ml.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The serious adverse event requiring hospitalization for Subject #65 and 101 was not due to the drug under investigation. Due to the accident, the subject # 65 (reference trt) has the last six (6) samples missing while the subject # 101(reference trt) had last seven (7) samples missing. The DBE calculated AUC (0-1656 hrs) and AUC (0-1824 hrs) from the reference mean plasma profile which were 85% and 81% of the AUC (0-2856) from the mean reference plasma profile. The DBE also computed the reference mean AUC (0-t) by including these two subjects. The T/R ratio of the arithmetic means of AUC (0-t) changed from 0.9567 to 0.9619. The DBE is aware of the fact that the actual AUC (0-t) values for these two subjects may be different from the values calculated above. For that reason it is essential that you provide the DBE with the plasma data and values of PK parameters for these two subjects. Moreover, from the plasma profiles we will determine whether these two subjects have feasible AUC (0-inf) values. Additionally, these two subjects will provide accurate values for Cmax and therefore the inclusion of these two subjects is essential for the statistical analysis of the Cmax value. Thus, based on our calculations, the DBE does not believe the inclusion of those subjects would result in an inaccurate and biased assessment of Cmax (definitely) and AUC (0-t), AUC (0-inf) (possibly). Therefore, you are requested to provide plasma data for these two subjects and provide statistical analyses of the PK parameters including these two (2) subjects.
3. You did not provide dissolution data for 12 individual dosage units (a Prefilled Syringe or a Vial is an individual dosage unit). The DBE requests the following additional information:

- a. Please, provide dissolution data for 12 individual dosage units using the method you have proposed in this submission: Please, submit the mean percent dissolution, CV% and range (minimum and maximum) of the dissolution.
- b. Please repeat the dissolution testing using your proposed method but with the paddle speed at 25 rpm.
- c. Please use additional sampling times at 12 hrs and 24 hrs in Sections "a" and "b" above.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ORIG AMENDMENT

AB

April 15, 2004

Mr. Gary Buehler
FDA/OGD/CDER
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553

BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to SICOR's amendment dated February 20, 2004. Further reference is made to the Agency's facsimile dated March 30, 2004.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide additional **bioequivalency** information requested.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District

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APR 16 2004

OGD / CDER



PHARMACEUTICALS, INC.

ORIGINAL

41



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Irvine, CA 92618
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Fax: 949.855.8210
www.sicor.com

May 17, 2004

ORIG AMENDMENT

N/A/M

Mr. Gary Buehler
OGD/CDER/FDA
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to our amendment dated October 16, 2003. Reference is also made to the Agency's facsimiles dated December 1, 2003 and December 12, 2003. Further reference is made to the conversation of May 11, 2004 between Peter Chen, of the Agency, and myself.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested.

Requested Item	Attachment
Dissolution method	1
Validation report for dissolution method	2
Updated Finished Product Specifications and Data Sheet	3
Dissolution Data for Medroxyprogesterone (Lot X01P613) at 29 months	4

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson
Director, Regulatory Affairs

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cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District

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MAY 18 2004

OGD/CDER

May 20, 2004

ORIG AMENDMENT

N/A

Mr. Gary Buehler
OGD/CDER/FDA
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553**

TELEPHONE AMENDMENT

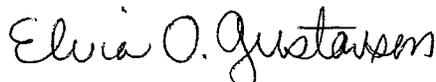
Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to our amendment dated October 16, 2003. Reference is also made to the Agency's facsimiles dated December 1, 2003 and December 12, 2003. Further reference is made to the conversation of May 11, 2004 and May 20, 2004 between Peter Chen, of the Agency, and myself.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested. Specifically, we are providing the Commercial Stability Protocol with the testing for dissolution as an attachment to this amendment.

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,



Elvia O. Gustavson
Director, Regulatory Affairs

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Attachment

cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District

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MAY 21 2004

OGD/CDER



PHARMACEUTICALS, INC.



19 Hughes
Irvine, CA 92618
Toll Free: 800.729.9991
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www.sicor.com

May 26, 2004

Mr. Gary Buehler
OGD/CDER/FDA
Metro Park North II, HFD-600
Attention: Documentation and Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Medroxyprogesterone Acetate Injectable
Suspension, USP, 150 mg/mL
ANDA No. 76-553

TELEPHONE AMENDMENT

ORIG AMENDMENT

N/A

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to our amendment dated October 16, 2003. Reference is also made to the Agency's facsimiles dated December 1, 2003 and December 12, 2003. Further reference is made to the conversation of May 26, 2004 between Kenneth Furnkranz, of the Agency, and myself.

In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested. Specifically, we are providing the revised Finished Product Specifications and Data Sheet (**Attachment 1**) and Commercial Stability Protocol reflecting the revised dissolution test specification (**Attachment 2**).

We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Elvia O. Gustavson

Elvia O. Gustavson
Director, Regulatory Affairs

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MAY 27 2004

OGD / CDER

Attachment

cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District

19 Hughes
 Irvine, CA 92618
 Toll Free: 800.729.9991
 Telephone: 949.455.4700
 Fax: 949.855.8210
 www.sicor.com

June 22, 2004

Mr. Gary Buehler
 OGD/CDER/FDA
 Metro Park North II, HFD-600
 Attention: Documentation and Control Room 150
 7500 Standish Place
 Rockville, MD 20855-2773

ORIG AMENDMENT

N/AM

**RE: Medroxyprogesterone Acetate Injectable
 Suspension, USP, 150 mg/mL
 ANDA No. 76-553**

TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to SICOR's ANDA 76-553 for Medroxyprogesterone Acetate Injectable Suspension, USP, 150 mg/mL, which was submitted to the Agency on November 27, 2002. Reference is also made to the telephone conversation of June 18, 2004 between Mr. Mike Smela, FDA, and Sonia Hernandez, Sicor Pharmaceuticals, Inc.

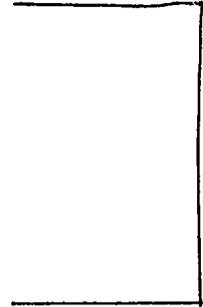
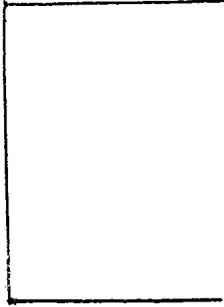
In accordance with the provisions of Section 314.96(a) of the *Code of Federal Regulations, Title 21*, we hereby amend our application to provide the additional **chemistry** information requested. Specifically, the specification for the Related Compounds, % have been revised for the release and shelf specifications. The revised **Finished Product Test Specification and Data Sheet** is enclosed. The original and revised specifications for Related Compounds, % are listed below:

	Original Specification		Current Specification	
	Release	Shelf	Release	Shelf
A. Medroxyprogesterone				
H. Total				

JUN 23 2004

OGD / CDER

Mr. Gary Buehler
Page 2
June 22, 2004



We trust you will find the information in this amendment satisfactory for your review and approval. If there are any questions concerning this amendment, please do not hesitate in contacting me at (949) 455-4724. We can also be contacted by facsimile at (949) 583-7351.

Sincerely,

Rosalie C. Lowe

for Elvia O. Gustavson
Director, Regulatory Affairs

S:\Medroxyprogesterone76553-vial\Amends\Amend 11 telephone.doc

Enclosure

cc: Mr. Alonza Cruse, District Director
FDA/Los Angeles District