64142

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64142

Trade Name Nystatin Oral Suspension USP, 100,000 Units/ml

Generic Name Nystatin Oral Suspension USP, 100,000 Units/ml

Sponsor UDL Laboratories, Inc.,

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 64142

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64142

APPROVAL LETTER

ANDA 64-142

JUN 25 1998

UDL Laboratories, Inc.
Attention: Dina Kostakis
7265 Ulmerton Road
Largo, FL 33771

Dear Madam:

This is in reference to your abbreviated new drug application dated December 5, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nystatin Oral Suspension USP, 100,000 Units/mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated September 25, 1997; and March 9, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nystatin Oral Suspension USP, 100,000 Units/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mycostatin® Oral Suspension, 100,000 Units/mL, of Apothecon, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

6-25-98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

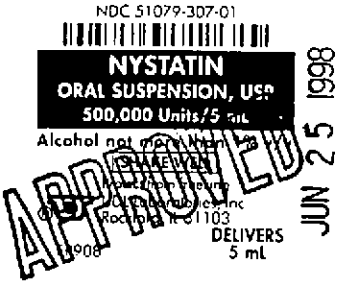
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64142

FINAL PRINTED LABELING

Nystatin Oral Suspension, USP
AADA 64-142
UDL Laboratories, Inc.

Container Label



Tray (Carton) Label

NDC 51079-307-11 JUN 25 1998

NYSTATIN
ORAL SUSPENSION, USP
500,000 Units/5 mL

SHAKE WELL

10 Unit-Dose Cups of 5 mL Each

Each mL, for oral administration, contains 100,000 units of nystatin. Alcohol (not more than 1% v/v). In addition, each mL contains the following inactive ingredients: benzaldehyde, carboxymethylcellulose sodium, citric acid, sodium phosphate, flavoring, glycerin, methylparaben, monobasic sodium phosphate, propylparaben, purified water, saccharin sodium and sucrose (50% w/v).

APPROVED

USUAL DOSAGE: See package insert for dosage information.

CAUTION: *Federal law prohibits dispensing without prescription.*

Keep this and all drugs out of the reach of children.

Store at controlled room temperature 15°–30°C (59°–86°F). Protect from freezing.

See bottom of container for lot number and expiration date.

UDL Laboratories, Inc.
Rockford, IL 61103 FP909

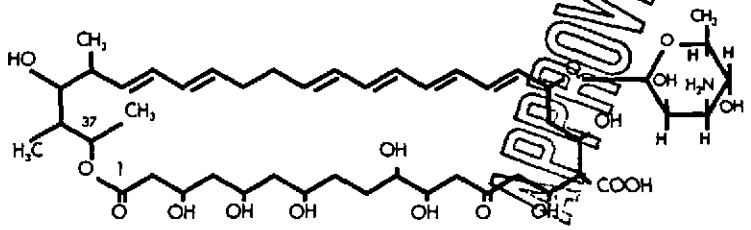
FP912 R2

NYSTATIN
ORAL SUSPENSION, USP

DESCRIPTION

Nystatin is an antimycotic polyene antibiotic obtained from *Streptomyces noursei*.

The structural formula is:



$C_{47}H_{75}NO_{17}$ MW 926.13

Each mL, for oral administration, contains 100,000 units of nystatin. Alcohol (not more than 1% v/v). In addition, each mL contains the following inactive ingredients: carboxymethylcellulose sodium, dibasic sodium phosphate, flavoring, glycerin, methylparaben, monobasic sodium phosphate, propylparaben, purified water, saccharin sodium and sucrose (50% w/v).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Gastrointestinal absorption of nystatin is insignificant. Most orally administered nystatin is passed unchanged in the stool. In patients with renal insufficiency receiving oral therapy with conventional dosage form, significant plasma concentrations of nystatin may occasionally occur.

Microbiology

Nystatin is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeast-like fungi. *Candida albicans* demonstrates no significant resistance to nystatin *in vitro* on repeated subculture in increasing levels of nystatin; other *Candida* species become quite resistant. Generally, resistance does not develop *in vivo*. Nystatin acts by binding to sterols in the cell membrane of susceptible *Candida* species with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin exhibits no appreciable activity against bacteria, protozoa, or viruses.

INDICATIONS AND USAGE

Nystatin oral suspension is indicated for the treatment of candidiasis in the oral cavity.

CONTRAINDICATIONS

The preparation is contraindicated in patients with a history of hypersensitivity to any of its components.

PRECAUTIONS

General

This medication is not to be used for the treatment of systemic mycoses. Discontinue treatment if sensitization or irritation is reported during use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential. There also have been no studies to determine mutagenicity or whether this medication affects fertility in males or females.

Pregnancy: Teratogenic Effects

Category C. Animal reproduction studies have not been conducted with nystatin oral suspension. It is also not known whether nystatin oral suspension can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nystatin oral suspension should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nystatin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nystatin is administered to a nursing woman.

Pediatric Use

See **DOSAGE AND ADMINISTRATION.**

012A

ADVERSE REACTIONS

Nystatin is well tolerated even with prolonged therapy. Oral irritation and sensitization have been reported. (See **PRECAUTIONS: General.**)

Gastrointestinal: Diarrhea (including one case of bloody diarrhea), nausea, vomiting, gastrointestinal upset/disturbances.

Dermatologic: Rash, including urticaria has been reported rarely. Stevens-Johnson syndrome has been reported very rarely.

Other: Tachycardia, bronchospasm, facial swelling, and nonspecific myalgia have also been rarely reported.

OVERDOSAGE

Oral doses of nystatin in excess of five million units daily have caused nausea and gastrointestinal upset. There have been no reports of serious toxic effects or superinfections (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

DOSAGE AND ADMINISTRATION

INFANTS: 2 mL (200,000 units of nystatin) four times daily (in infants and young children, use dropper to place one-half of dose in each side of mouth and avoid feeding for 5 to 10 minutes).
NOTE: Limited clinical studies in premature and low birth weight infants indicate that 1 mL four times daily is effective.

CHILDREN AND ADULTS: 4–6 mL (400,000 to 600,000 units nystatin) four times daily (one-half of dose in each side of mouth). The preparation should be retained in the mouth as long as possible before swallowing.

Continue treatment for at least 48 hours after perioral symptoms have disappeared and cultures demonstrate eradication of *Candida albicans*.

Shake well before use.

HOW SUPPLIED

Nystatin Oral Suspension, USP is available as a cherry flavored, light creamy yellow, ready-to-use suspension containing 100,000 units nystatin per mL. It is supplied as follows:

NDC 51079-307-10 — Unit dose cups of 5 mL, in cartons of 50
(5 trays of 10 unit dose cups each)

Storage

Store at controlled room temperature 15°–30°C (59°–86°F). Avoid freezing.

Caution: Federal law prohibits dispensing without prescription.

UDL Laboratories, Inc.
Rockford, IL 61103

FP912 R2
Rev. 1/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64142

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #7 (revised)

2. ANDA #64-142

3. NAME AND ADDRESS OF APPLICANT

UDL Laboratories, Inc.
Attention: Dina Kostakis
7265 Ulmerton Road
Largo, FL 33771

Phone: 813-530-1633
Fax: 813-531-5427

4. LEGAL BASIS FOR SUBMISSION

21 CFR §449.150b
Reference drug: MYCOSTATIN® ORAL SUSPENSION (Nystatin Oral Suspension, USP) manufactured by E.R. Squibb & Sons, Inc. (Apothecon is the current holder)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Nystatin Oral Suspension, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission: 12/5/94
Acknowledgment: 1/11/95
N/A letter (MINOR): 5/12/95
Amendment: 6/27/95
Amendment 4/4/97 to N/A letter (MAJOR) 10/6/95
Amendment 9/18/97 to N/A letter (FACSIMILE) 8/21/97
Amendment 9/25/97 (Telephone Amendment for BIO issue)
Amendment 11/11/97 to N/A letter (MINOR) 10/23/97
Amendment 3/9/98 to N/A letter (FACSIMILE) 1/12/98

10. PHARMACOLOGICAL CATEGORY

Antifungal

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Oral Suspension

14. POTENCY

500,000 u/5 mL
(10 mL package withdrawn in Amendment 6/27/95)

15. CHEMICAL NAME AND STRUCTURE

$C_{47}H_{75}NO_{17}$ MW = 926.13
(see CR #1)

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. In Amendment 4/4/97, to answer N/A (MAJOR) letter 10/6/95 (concentration of [redacted] exceeds the previously approved in a pharmaceutical dosage form for the same route of administration), Firm has reformulated the Nystatin Oral Suspension by removing [redacted] from the originally proposed drug product and increasing the parabens from [redacted] methylparaben and [redacted] propylparaben to [redacted] and [redacted], respectively. Firm submits revised chemistry, manufacturing, controls and labeling information in the amendment.

CR #4 supersedes the previous reviews unless otherwise indicated.

B. Amendment 3/9/98 Firm answers in order:

Q1. On page 414 (Product Reconciliation Form in the batch records) of your Amendment dated 4/4/97, under Packaging Accountability, we note that "Avg. Fill Volume" is listed as [redacted] It is not clear how this value was obtained since the [redacted] was set at [redacted] and the record on page 404 verified the limits. Please explain.

A1. The Average Fill Volume and Average Delivery Volume are two different processes within the filling operation. Average Fill Volume is the amount of the product that is placed within the unit dose cup at the filling stage. Average Delivery Volume is the amount of the product that is delivered from the unit dose cup. Average Delivery Volume obtained for lot 606046 ranged from [redacted] and fall within the established specifications of [redacted] The calculations are provided.

Q2. Your samples have been tested by our laboratory and found to have a potency which exceeds the upper limit:

Results:

Nystatin (100,000 u/mL, l.c.)
Container 5 - 139,000
Container 6 - 141,000
Container 7 - 133,000
Avg 3 = 137,700 u/mL (137.7% of l.c.)
Potency limit: 90.0 - 130.0% (USP)

a. Our laboratory used one mL of sample from each container for the assay procedure. We are not certain how you prepared samples for the potency assay. Did you follow the same sample preparation procedure as described under UNIFORMITY OF DOSAGE UNITS on page 493 of the Amendment dated April 4, 1997? Please clarify.

b. Please comment on our laboratory findings.

A2. UDL used two different outside testing laboratories [redacted] for assaying the potency of Lot #606046. Both laboratories show correlatable results within expected assay variability and the assay specification for Nystatin of 90.0 - 130.0% (USP). Results are

provided.

The laboratories conduct the test from a composite sample provided by UDL. The composite for finished product testing is prepared by UDL laboratories prior to sending to the outside testing laboratory. The composite is prepared by shaking well, a sufficient number of unit-dose cups, one at a time, and pouring the contents into a sample bottle for the composite. A portion of the same composite sample is used to perform the Uniformity of Dosage Unit and test for Uniformity of Dosage Unit.

Firm comments that it is critical to perform ample shaking of the cup as well as pipet the sample immediately after shaking. Either one of these factors could contribute to a higher biased assay. UDL is willing to communicate with the FDA laboratory to discuss the test method and offer its assistance.

Comments:

1. The bulk supplier is acceptable per 5/15/98 recommendation (see report dated 6/11/98).

2. The finished product and stability specifications, and testing procedures have been revised to include dissolution testing according to the requested test parameters and specifications.

3. The additional samples sent by UDL in April 1998 are still under review. Since this is a compendial drug product, it does not need to be tested by our District Laboratories under current policy. Nystatin is absorbed very sparingly following oral administration, with no detectable blood levels when given in the recommended doses. Most of the orally administered nystatin is passed unchanged in the stool. It should not pose any safety issue even though our lab found the previous samples to exceed the potency limits (Avg. 137.7% of label claim; USP 90.0-130.0%).

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih
DATE COMPLETED: 3/16/98 (revised 6/11/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64142

BIOEQUIVALENCE REVIEW(S)

[redacted]

2.1

9.25.97 Sabra

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 64-142 APPLICANT: UDL Laboratories, Inc.

DRUG PRODUCT: Nystatin Oral Suspension, 100,000 U/ml

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.2% sodium lauryl sulfate at 37°C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than__ __ (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 64-142
ANDA DUPLICATE
DIVISION FILE
HFD-650/Division Sign Off
HFD-650/Jackson
BIO DRUG FILE
FIELD COPY

Dates :- 4 APR 97
- 25-SEP-97

64142 dwc. 497

(X:NEW\FIRMSNZ\UDL\LTRS&REV\~~64142bio.fdw~~)

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

2. **FOOD STUDY** (STP)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

3. **MULTIPLE DOSE STUDY** (STM)

   Clinical: _____
   Analytical: _____

   Strengths: _____

   Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS)

   All Strengths

   Outcome: AC IC UN NC

5. **STUDY AMENDMENT** (STA)

   Strengths: 100,000 u/ml

   Outcome: (AC) IC UN NC

6. **WAIVER** (WAI)

   Strengths: _____

   Outcome: AC IC UN NC

7. **DISSOLUTION WAIVER** (DIW)

   Strengths: _____

   Outcome: AC IC UN NC

8. **OTHER** (OTH) _____

   Strengths: _____

   Outcome: AC IC UN NC

9. **OTHER OPTIONS** (less common):
   a. Protocol (PRO)
   b. Protocol Amendment (PRA)
   c. Protocol/Dissolution (PRD)

   Strengths: _____
   d. Special Dosage (STS)
   e. Study/Dissolution (STD)
   f. Bio study (STU)
   Outcome: AC IC UN NC

OUTCOME DECISIONS:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

Nystatin
Oral Suspension
100,000 U/ml
AADA # 64142
Reviewer: A.J. Jackson
WP # 64142DWC.497

UDL Laboratories
Largo, Florida
Submission Dated:
April 4, 1997
September 25, 1997

Review of Dissolution Data and a Request for a Waiver

The firm submitted a waiver request for their 100,000 U/ml oral suspension on December 5, 1994. The waiver was denied since the solution was not qualitatively and quantitatively the same as the reference and the firm used the incorrect dissolution medium. Deficiencies from the earlier submission are addressed in the current application and the firm has also reformulated their product. The amendment submitted on 9/25/97 contains the additional dissolution data in 0.2% sodium lauryl sulfate at 50 and 75 rpm(paddle).

Comment 1:

The composition of your product lists _____ as an **inactive ingredient, the concentration** of which exceeds that previously approved in a pharmaceutical dosage form for the same route of administration.

As provided under 21 CFR 314.94(a)9(ii), an applicant shall identify and characterize the inactive ingredients in their proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.

> Unless data are presented that satisfies the provisions of 21 CFR 314.94 as expressed above, it is the position of the Office that the test product will need to be reformulated by either removing or reducing the concentration of benzaldebyde.

Response to Comment 1:

UDL has reformulated the Nystatin Oral Suspension by removing the _____ from the proposed original drug product and increasing the parabens from _____ methylparaben and _____ propylparaben to _____ and _____ respectively. Revised chemistry, manufacturing, controls (CMC)

and labeling information are included in this response. It should be noted that except for the formulation and corresponding stability batch related data, the information submitted in the original AADA still applies. A table of contents precedes the revised CMC and labeling information. The table of contents indicates the sections of the AADA updated due to the reformulation as well as procedures or specifications updated since the last submission of December 5, 1994 and amendments of June 27 and July 24, 1995. Where applicable, page references to the original AADA are cited.

Comment 2.

Comparative dissolution data for the product are present in the application using 0.2% sodium dodecyl sulfate (paddle, 50 rpm). Analytical information is necessary to support the dissolution and validate the assay methodology used in this application. Future submissions on this product should develop a dissolution profile by collecting samples at 15, 30, 45 and 60 minutes.

Response:

The dissolution methodology indicated in Comment 2 will not be used based on the results found in response to Comment 3.

Comment 3:

Dissolution testing should also be conducted on 12 samples of the test product versus 12 samples of the reference product using the following methods "A" and "B":

Method A:

Apparatus:	USP XXIII Paddle
RPM:	25
Distance from bottom:	2.5 cm
Volume:	900 ml
Medium:	0.05% Sodium Lauryl Sulfate
Sampling Times:	15, 30, 45 and 60 minutes

Method B:
Same as method "A" except that the concentration of sodium lauryl sulfate in the dissolution medium should be 0.1%.

Response:

Comparative dissolution of UDL Laboratories, Nystatin oral suspension, USP 100,000 U/ml and Mycostatin oral suspension 100,000 U/ml performed by indicated methods "A"

and "B".

COMPOSITION OF REFERENCE NEW AND OLD TEST FORMULATIONS STATEMENTS

Table 1. Comparative Formulations

	Nystatin(new-Test)	Nystatin(old-Test)	Mycostatin
	per ml	per ml	per ml
Nystatin USP	110,000* U	100,000 U	100,000 U
Methylparaben NF			
Propylparaben NF			
Alcohol(Ethyl 190 Proof) USP			
Carboxymethyl-cellulose Sodium USP			
Saccharin Sodium USP			
Sucrose NF			
Monobasic Sodium Phosphate, Monohydrate USP			
Dibasic Sodium Phosphate, Heptahydrate USP			
Glycerin USP			
Peppermint Oil			
Cinnamaldehyde			
Flavor Imitation Cherry			
Sodium Phosphate			

Sodium Hydroxide	
Artificial Wild Cherry	
Purified Water	

* An excess of 10% is allowed due to the variation of the raw material assay and targeted to be within mid-range of the USP specification for the product. The commercial batches will be made with 10% excess of Nystatin. The stability batch was made with 115% excess. See pages 24A to 24C of this amendment for justification.

Comments:

1.The ingredients for the test formulation methylparaben, propylparaben and ethyl alcohol which have concentrations different from the reference are within the ranges listed in the 1996 inactive ingredients guide. Comparisons are as follows:

Ingredient	Page	Range	Test	Reference
a. Methylparaben	82			
b. Propylparaben	118			
c.190 proof ethyl alcohol	3			

The propylparaben which is 0.01% over the range listed in the inactive ingredients guide is used as a preservative in food and as an antifungal in pharmaceuticals and it is unlikely that such a small increase will present toxicity problems.

The other differences are related to flavors which should not impact the product's bioequivalence.

2. The dissolution data presented in Tables 2 and 3 are acceptable.

3. The product lists an overage of 10% which is supported by the 3 month accelerated testing done by the firm. In addition page 1111 of USP 23 lists that the product should contain not less than 90% and not more than 140% of the labeled amount of USP Nystatin Units.

Recommendation:

1. The dissolution testing conducted by UDL Laboratories on their nystatin oral suspension, batch #606046, is acceptable.

2. The Division of Bioequivalence finds that the information submitted by UDL Laboratories demonstrates that nystatin oral suspension (100,000 units/ml) falls under 21 CFR 320.24 (b)(6) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the

waiver of an in-vivo bioavailability study be granted. UDL Laboratories' test product is deemed bioequivalent to Mycostatin[R] oral suspension (100,000 units/ml) manufactured by E.R. Squibb.

3. From the bioequivalence point of view the firm has met the in-vitro dissolution requirements and the application is acceptable.

4. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.2% sodium laurly sulfate at 37 C using USP apparatus II paddle at 50 rpm. The test product should meet the following specifications:

Not less thar____ of the labelled amount of the drug in the dosage form is dissolved in 60 minutes.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG Date: 11/13/97

Concur: 11/18/97 Date:_____
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: AADA# 64-142DW.497 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File,HFD-650(director)

Table 2 . In Vitro Dissolution Testing

Drug (Generic Name):Nystatin Oral Suspension
Dose Strength:100,000 U/ml
ANDA No.:61-142
Firm:UDL Laboratories
Submission Date:April 4, 1997
File Name:61142DWC.497

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 25
Volume:900 ml 0.05% Sodium Lauryl Sulfate
Specifications: Dissolution profile
Units: 12
Reference Drug: Mycostatin
Assay Methodology

Results of In Vitro Dissolution Testing:0.05% Sodium Lauryl Sulfate

Sampling Times (Minutes)	Test Product Lot # 606046 Strength(U) 100000			Reference Product Lot # MA001 Strength(mg) 100000		
	Mean %	Range	%CV	Mean %	Range	%CV
15	4.87		2.34	5.92		1.46
30	4.98		1.73	5.99		1.68
45	5.06		2.53	6.08		1.07
60	5.14		2.04	6.17		1.29

Results of In Vitro Dissolution Testing:0.1% Sodium Lauryl Sulfate

Sampling Times (Minutes)	Test Product Lot # 606046 Strength(U) 100000			Reference Product Lot # MA001 Strength(mg) 100000		
	Mean %	Range	%CV	Mean %	Range	%CV
15	6.35		4.71	8.13		2.93
30	6.62		3.56	8.34		3.64
45	6.80		2.84	8.59		2.48
60	6.93		3.34	8.74		2.52

Table 3 . In Vitro Dissolution Testing

Drug (Generic Name):Nystatin Oral Suspension
Dose Strength:100,000 U/ml
ANDA No.:61-142
Firm:UDL Laboratories
Submission Date:April 4, 1997
File Name:61142DWC.497

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50
Volume:900 ml 0.2% Sodium Lauryl Sulfate
Specifications: Dissolution profile
Units: 12
Reference Drug: Mycostatin
Assay Methodology:

Results of In Vitro Dissolution Testing:0.2% Sodium Lauryl Sulfate

Sampling Times (Minutes)	Test Product Lot # 606046 Strength(U) 100000			Reference Product Lot # MA001 Strength(mg) 100000		
	Mean %	Range	%CV	Mean %	Range	%CV
15	26		4.44	24.1		2.49
30	29.3		2.03	23.8		1.56
45	29.5		1.35	24.0		
60	29.6		0.79	24.1		1.25

Results of In Vitro Dissolution Testing:0.2% Sodium Lauryl Sulfate-75 RPM

Sampling Times (Minutes)	Test Product Lot # 606046 Strength(U) 100000			Reference Product Lot # MA001 Strength(mg) 100000		
	Mean %	Range	%CV	Mean %	Range	%CV
15	27.0		1.74	23.6		3.41
30	27.4		2.21	24.1		3.29
45	27.3		1.89	24.6		4.45
60	27.1		1.55	24.7		3.71

TELEPHONE MEMO

To: Dina Kostakis
UDL Laboratories
(813) 530-1633

REF # ANDA 64-142

From: Lizzie Sanchez

Date: 8/27/97

Subject: **Nystatin Oral Suspension**

Requested by: Andre Jackson

Ms. Kostakis was contacted to request additional dissolution data using the same testing conditions but including:

0.2% Sodium Lauryl Sulfate
at 50 rpm and also at 75 rpm

Please label as a telephone amendment. You may fax your response and follow with a hard copy.

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531- 5427
(813) 530-1633

FAX MACHINE COVER PAGE

DATE: 9/25/97 **NUMBER OF PAGES INCLUDING COVER PAGE** 11

TO WHOM SENT Lizzie Sanchez

COMPANY NAME FDA - Bioequivalence

FAX NUMBER (301) 594-0181

FROM Dina Kostakis

COMMENTS Refax of entire Amendment to AADA 64-142. Correction to page 8; typing error of "5" minutes chnaged to 15. Please call Dina Kostakis at (813) 530-1633 if there are any questions.

SHOULD YOU HAVE ANY PROBLEMS RECEIVING THIS TELECOPY, PLEASE CALL.

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531-5427
(813) 530-1633

FAX MACHINE COVER PAGE

DATE: 9/25/97 **NUMBER OF PAGES INCLUDING COVER PAGE** 14

TO WHOM SENT Lizzie Sanchez

COMPANY NAME FDA - Bioequivalence

FAX NUMBER (301) 594-0181

FROM Dina Kostakis

COMMENTS TELEPHONE AMENDMENT to Agency Teleconference of August 27, 1997

A hard copy of the response is overnighted.

Please call Dina Kostakis at (813) 530-1633 if there are any questions.

SHOULD YOU HAVE ANY PROBLEMS RECEIVING THIS TELECOPY, PLEASE CALL.

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 3377
FAX (813) 531-542
(813) 530-163

September 25, 1997

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metrol Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

NYSTATIN ORAL SUSPENSION, USP
100,000 U/ML
AADA 64-142
RESPONSE TO TELECONFERENCE
DATED AUGUST 27, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated Antibiotic Drug Application identified above and to the Agency's teleconference between Ms. Lizzie Sanchez of the Food and Drug Administration and Ms. Dina Kostakis, on August 27, 1997. Ms. Sanchez related an additional request from the Bioequivalence reviewer in relation to the dissolution data submitted in the Nystatin Oral Suspension Amendment dated April 4, 1997. The Bioequivalence reviewer requested additional dissolution data using 0.2% Sodium Dodecyl Sulfate at 50 and 75 rpm with sampling times of 15, 30, 45 and 60 minutes, using the same USP 23 paddle as used previously in the April 4, 1997 amendment.

In response to the Agency's August 27, 1997 teleconference request, UDL wishes to amend the application with the following:

ADDITIONAL DISSOLUTION DATA:

FDA COMMENT: Provide additional dissolution data using 0.2% Sodium Dodecyl Sulfate at 50 and 75 rpm with sampling times of 15, 30, 45 and 60 minutes, using a USP 23 paddle apparatus.

UDL RESPONSE: At the FDA's request, UDL has obtained dissolution data using 0.2% Sodium Dodecyl Sulfate medium at 50 and 75 rpm with sampling times of 15, 30, 45 and 60, using a USP 23 paddle apparatus. The data are provided in Attachment A.

The enclosed Table of Contents outlines the documentation being submitted in support of this amendment. A Form FDA 356h is immediately following the Table of Contents.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact the undersigned by phone at (813) 530-1633, or by facsimile at (813) 531-5427.

Sincerely,

Dina Kostakis

DINA KOSTAKIS
Director of Quality

DK/mg

Attachment(s)

AUG 3 1995

Nystatin
Oral Suspension
100,000 U/ml
AADA # 64142
Reviewer: A.J. Jackson
WP # 64142DW.D94

UDL Laboratories
Largo, Florida
Submission Dated:
December 5, 1994

Review of Dissolution Data and a Request for a Waiver

The firm is requesting a waiver of the in-vivo bioequivalene requirements for their nystatin 100,000 U/ml suspension. In support of their request the firm has submitted dissolution data comparing the product to the reference listed product Mycostatin by E.R. Squibb. The firm has also submitted the formulation for their product.

Comments:

1.The firm has submitted comparative dissolution data for their product using 0.2% sodium dodecyl sulfate (paddle, 50 rpm). The firm should supply validation information to support their dissolution and assay methodology. Future submissions on this product should develop a dissolution profile by collecting samples at 15, 30, 45 and 60 minutes.

2.Also for any future submissions, the firm is advised to conduct additional dissolution testing on 12 samples of the test product versus 12 samples of the reference product using the following methods "A" and "B":

Method A:

Apparatus:	USP XXIII Paddle
RPM:	25
Distance from bottom:	2.5 cm
Volume:	900 ml
Medium:	0.05% Sodium Lauryl Sulfate
Sampling Times:	15, 30, 45 and 60 minutes

Method B:
Same as method "A" except that the concentration of sodium lauryl sulfate in the dissolution medium should be 0.1%.

3.The comparative formulations for the test and reference products are given in Table 1.

Table 1. Comparative Formulations

	Nystatin (test)	Mycostatin(ref)
	per ml	per ml
Nystatin USP	100,000 U	100,000 U
Methylparaben NF		
Propylparaben NF		
Alcohol(Ethyl 190 Proof) USP		
Carboxymethyl-cellulose Sodium USP		
Saccharin Sodium USP		
Sucrose NF		
Monobasic Sodium Phosphate, Monohydrate USP		
Dibasic Sodium Phosphate, Heptahydrate USP		
Glycerin USP		
Peppermint Oil		
Cinnamaldehyde		
Flavor Imitation Cherry		
Sodium Phosphate		
Sodium Hydroxide		
Artificial Wild Cherry		
Purified Water		

Deficiency:

The formulation for the test product contains the ingredient _____ which is not in the reference formulation and at a higher concentration than that is listed in the inactive ingredients guide for oral suspensions.

Recommendation:

1.The formulation for the test product is not equivalent to that for the reference product Mycostatin. The dissolution testing conducted by the firm on its nystatin oral suspension, 100,000 U/ml, lot # 402022 has been found to be unacceptable, therefore the waiver of in-vivo bioequivalence study requirements for the test product cannot be granted until acceptable formulation and dissolution data has been submitted. The firm should receive deficiency and comments 1 and 2.

2.From the bioequivalence point of view the firm has not met the in-vitro dissolution requirements and the application is unacceptable.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG _____ Date: 8/1/95
8/3/95

cc: AADA# 64-142DW.D94 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

AJJ/072795/dbm/WP#64142DW.D94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64142

CORRESPONDENCE

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

June 27, 1995

ARCHIVAL COPY 6/28/95

Mr. Douglas Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: **Nystatin Oral Suspension, USP**
AADA 64-142 MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to the Administration's letter dated May 12, 1995 regarding the Nystatin Oral Suspension AADA submitted on behalf of UDL Laboratories, Inc. by Lachman Consultant Services, Inc. as Agent.

This **Minor Amendment** constitutes our response to that letter. A summary detailing the contents of this amendment immediately follows Form FDA 356h. A field copy certification statement is also provided.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Mary-Anne D'Esposito for

Leon Lachman, Ph.D.
President

Enclosure

RECEIVED
JUN 27 1995
C DRUGS

83E5178

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531- 5427
(813) 530-1633

BIOAVAILABILITY
ORIG AMENDMENT

ARCHIVAL COPY

March 9, 1998

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

N/A

Noted
To Maria S.

CMC Data Enclosed
Bioequivalence Data Enclosed

MINOR AMENDMENT

NYSTATIN ORAL SUSPENSION, USP
100,000 UNITS/ML
AADA 64-142
RESPONSE TO AGENCY'S
CORRESPONDENCE
DATED JANUARY 12, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated Antibiotic Drug Application identified above and to the Agency's correspondence provided via facsimile on January 12, 1998. In response to the Agency's January 12, 1998 comments, UDL wishes to amend the application with the following:

A. REGARDING CHEMISTRY ISSUES:

MAR 10 1998

GENERIC DRUGS

3-11-98

B. REGARDING OTHER ISSUES:

FDA COMMENT: In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

All facilities involved in the manufacture of this finished product must be in compliance with current good manufacturing practice (CGMP) regulations. The application can not be approved if there are any CGMP issues pending.

UDL RESPONSE: It is noted and acknowledged that all facilities involved in the manufacture of this product must be in compliance with current good manufacturing practice (CGMP) regulations. It is acknowledged that the application can not be approved if there are any CGMP issues pending.

C. REGARDING BIOEQUIVALENCE REQUEST:

FDA COMMENT: The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.2% sodium lauryl sulfate at 37°C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than ____(Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

UDL RESPONSE: The finished product and stability specifications, and testing procedures have been revised to include dissolution testing according to the requested test parameters and specifications (See Attachment E). This procedure was utilized in the testing performed for the data provided in the September 25, 1997 Bioequivalence Amendment.

For you reference a copy of the Agency letter dated January 12, 1998 is enclosed in Attachment F.

As required by 21 CFR 314.96(c), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to FDA's Orlando District Office.

The enclosed Table of Contents outlines the documentation being submitted in support of this amendment. A Form FDA 356h is immediately following the Table of Contents.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact the undersigned by phone at (813) 530-1633, or by facsimile at (813) 531-5427.

Sincerely,

Dina Kostakis

Dina Kostakis
Director of Quality

DK/mg

Attachment(s)

ATTACHMENT F

AGENCY LETTER

OF

JANUARY 12, 1998

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531-5427
(813) 530-1633

November 11, 1997

NDA ORIG AMENDMENT
N/A m

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855-2773

Noted.
To M. Shah
11/14/97

ARCHIVAL COPY

MINOR AMENDMENT

NYSTATIN ORAL SUSPENSION, USP
100,000 UNITS/ML
AADA 64-142
RESPONSE TO AGENCY'S
CORRESPONDENCE
DATED OCTOBER 23, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated Antibiotic Drug Application identified above and to the Agency's correspondence provided via facsimile on October 23, 1997. In response to the Agency's October 23, 1997 comments, UDL wishes to amend the application with the following:

A. REGARDING CHEMISTRY ISSUES:

11-13-97

NOV 12 1997

GENERIC DRUGS

c:\dina\letters\spn64142

B. REGARDING OTHER ISSUES:

FDA COMMENT: In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

> All facilities involved in the manufacture of this finished product must be in compliance with current good manufacturing practice (CGMP) regulations. The application can not be approved if there are any CGMP issues pending.

UDL RESPONSE: It is noted and acknowledged that all facilities involved in the manufacture of this finished product must be in compliance with current good manufacturing practice (CGMP) regulations. It is acknowledged that the application can not be approved if there are any CGMP issues pending.

For your reference a copy of the Agency's letter dated October 23, 1997 is provided in Attachment B.

As required by 21 CFR 314.96(b), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to FDA's Orlando District Office.

The enclosed Table of Contents outlines the documentation being submitted in support of this amendment. A Form FDA 356h is immediately following the Table of Contents.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact the undersigned by phone at (813) 530-1633, or by facsimile at (813) 531-5427.

Sincerely,
UDL Laboratories, Inc. - Florida

Dina Kostakis

Dina Kostakis
Director of Quality

DK/mg

Attachment(s)

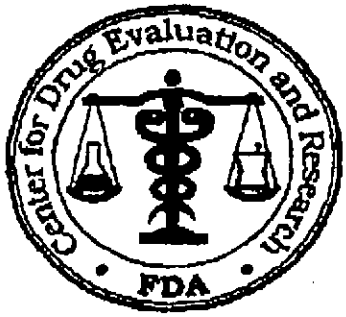
c:\dina\letters\spn64142

MINOR AMENDMENT

ATTACHMENT B

OCT 23 1997

AADA 64-142



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)

TO: APPLICANT: UDL Laboratories, Inc. PHONE: 813-530-1633

ATTN: Dina Kostakis FAX: 813-531-5427

FROM: Mark Anderson PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated antibiotic application dated December 5, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Nystatin Oral Suspension USP, *500,000 U/5 mL.*

Reference is also made to your amendments dated April 4, 1997 and September 18, 1997.

The application is deficient and, therefore, Not Approvable under Section 507 of the Act for the reasons provided in the attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, norwill the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\faxmin.frm

OCT 23 1997

38. Chemistry Comments to be Provided to the Applicant

AADA: 64-142

APPLICANT: UDL Laboratories, Inc.

DRUG PRODUCT: Nystatin Oral Suspension, USP

The deficiencies presented below represent MINOR deficiencies

A. Chemistry Deficiencies:

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

All facilities involved in the manufacture of this finished product must be in compliance with current good manufacturing practice (CGMP) regulations. The application can not be approved if there are any CGMP issues pending.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

2.1

TELEPHONE MEMO

To: Dina Kostakis
UDL Laboratories
(813) 530-1633

REF # ANDA 64-142

From: Lizzie Sanchez

Date: 8/27/97

Subject: **Nystatin Oral Suspension**

Requested by: Andre Jackson

Ms. Kostakis was contacted to request additional dissolution data using the same testing conditions but including:

0.2% Sodium Lauryl Sulfate
at 50 rpm and also at 75 rpm

Please label as a telephone amendment. You may fax your response and follow with a hard copy.

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531-5427
(813) 530-1633

September 18, 1997

ARCHIVAL COPY

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metrol Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

NYSTATIN ORAL SUSPENSION, USP
100,000 U/ML
AADA 64-142
RESPONSE TO FACSIMILE COMMENTS
DATED AUGUST 21, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated Antibiotic Drug Application identified above and to the Agency's correspondence provided via facsimile on August 21,1997. In response to the Agency's August 21, 1997 comments, UDL wishes to amend the application with the following:

A. REGARDING CHEMISTRY ISSUES:

As required by 21 CFR 314.96(b), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to FDA's Orlando District Office.

The enclosed Table of Contents outlines the documentation being submitted in support of this amendment. A Form FDA 356h is immediately following the Table of Contents.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact the undersigned by phone at (813) 530-1633, or by facsimile at (813) 531-5427.

Sincerely,

Dina Kostakis

DINA KOSTAKIS
Director of Quality

DK/mg

Attachment(s)

OCT 23 1997

38. Chemistry Comments to be Provided to the Applicant

AADA: 64-142

APPLICANT: UDL Laboratories, Inc.

DRUG PRODUCT: Nystatin Oral Suspension, USP

The deficiencies presented below represent MINOR deficiencies

A. Chemistry Deficiencies:

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

All facilities involved in the manufacture of this finished product must be in compliance with current good manufacturing practice (CGMP) regulations. The application can not be approved if there are any CGMP issues pending.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

AADA 64-142

OCT 23 1997

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)

TO: APPLICANT: UDL Laboratories, Inc. PHONE: 813-530-1633

ATTN: Dina Kostakis FAX: 813-531-5427

FROM: Mark Anderson PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated antibiotic application dated December 5, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Nystatin Oral Suspension USP, 500,000 U/5 mL.

Reference is also made to your amendments dated April 4, 1997 and September 18, 1997.

The application is deficient and, therefore, Not Approvable under Section 507 of the Act for the reasons provided in the attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, norwill the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\faxmin.frm

AUG 2 1 1997

38. Chemistry Comments to be Provided to the Applicant

AADA: 64-142

APPLICANT: UDL Laboratories, Inc.

DRUG PRODUCT: Nystatin Oral Suspension, USP

The deficiencies presented below represent FACSIMILE deficiencies

A. Chemistry Deficiencies:

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

AUG 2 1 1997

~~NDA~~/AADA: 64-142

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT UDL Laboratories PHONE 813-530-1633
ATTN: Dina Kostakis FAX 813-531-5427

FROM: Mark Anderson, PROJECT MANAGER (301-827-5848)

Dear ~~Sir~~/Madam:

This facsimile is in reference to your abbreviated ~~new drug~~/antibiotic application dated 12/5/94, submitted pursuant to Section ~~505(j)~~/507 of the Federal Food, Drug, and Cosmetic Act for Nystatin Oral Suspension, 100,000u/mL

Reference is also made to your amendment(s) dated April 4, 1997

Attached are 2 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You ~~have been~~/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

Labeling is satisfactory

X:\new\ogdadmin\faxtrak\faxcov.fax

UDL LABORATORIES, INC.
7265 Ulmerton Road Largo, FL 33771
FAX (813) 531- 5427
(813) 530-1633

Needs bio assignment
to evaluate new formulation
eligible for waiver M. Anderson 7/23/97

April 4, 1997

NDA ORIG AMENDMENT

ARCHIVAL

BIOAVAILABILITY

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

COPY

Subject: Nystatin Oral Suspension, USP
AADA 64-142 MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to the Administration's letters dated October 6, 1995 (see attached) and September 18, 1996 regarding the Nystatin Oral Solution AADA submitted on behalf of UDL Laboratories, Inc. by Lachman Consultant Services, Inc. as Agent.

This Major Amendment constitutes our response to those letters. A summary detailing the contents of this amendment immediately follows Form FDA 356h. As required by 21 CFR 314.96 (b), we certify that a field copy, which contains a true copy of the technical sections of this amendment, has been submitted to the Orlando, Florida District Office.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this amendment, please do not hesitate to contact the undersigned at (813) 530-1633.

Sincerely,
UDL Laboratories, Inc. - Florida

Dina Kostakis

DINA KOSTAKIS
Regulatory Affairs/Compliance Manager

DK/mg

Attachment

RECEIVED
RECEIVED Jun 7 1997
Jun 7 1997 GENERIC DRUGS
GENERIC DRUGS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AADA 64-142

Lachman Consultant Services, Inc.
Attention: Leon Lachman, Ph.D.
Agent for UDL Labs, Inc.
1600 Stewart Avenue
Westbury, NY 11590

OCT - 6 1995

Dear Sir:

This is in reference to your abbreviated antibiotic application dated December 5, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Nystatin Oral Suspension USP, 100,000 U/mL, 5 ml Unit-dose Cups.

Reference is also made to your amendments dated June 27 and July 24, 1995.

The application is not approvable under section 507 of the Act, since the data submitted has failed to demonstrate that the test product is bioequivalent to the reference listed drug for the following reasons [21 CFR §314.127(a)(6)(i)]:

1. The composition of your product lists _____ as an inactive ingredient, the concentration of which exceeds that previously approved in a pharmaceutical dosage form for the same route of administration.

   As provided under 21 CFR 314.94(a)(9)(ii), an applicant shall identify and characterize the inactive ingredients in their proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.

   Unless data are presented that satisfies the provisions of 21 CFR 314.94 as expressed above, it is the position of the Office that the test product will need to be reformulated by either removing or reducing the concentration of _____

2. Comparative dissolution data for the product are present in the application using 0.2% sodium dodecyl sulfate (USP apparatus II (paddle), at 50 rpm. Analytical information is necessary to support the dissolution and validate the assay methodology used in this application. Future submissions on this product should develop a dissolution profile by collecting samples at 15, 30, 45 and 60 minutes.

3. Dissolution testing, should also be conducted on 12 samples of the test product versus 12 samples of the reference product using the following methods "A" and "B":

Method A:

Apparatus:	USP 23 Paddle
Speed:	25 rpm
Distance from bottom:	2.5 cm
Volume:	900 ml
Medium:	0.05% Sodium Lauryl Sulfate
Sampling Times:	15, 30, 45 and 60 minutes

Method B:

Same as above except the concentration of sodium lauryl sulfate in the dissolution medium should be 0.1%.

The Office of Generic Drugs will suspend any further review of this application until an amendment containing complete information and data necessary to support your chosen plan of action is submitted to the Agency.

The file on this application is now closed. You are required to take an action described under 21 CFR §314.120 and 21 CFR §314.96, which will either amend or withdraw the application. Should you decided to amend the application, the amendment should respond to all the deficiencies listed. **In the event that reformulation of the test product is needed to meet the agency's bioequivalence requirements, revised chemistry, manufacturing, controls and labeling information should also be included in the amendment.** A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as a MAJOR AMENDMENT and should be so designated in your cover letter. The cover letter should clearly state what information is being provided in the submission (i.e., Chemistry, Bioequivalence, Labeling). If you should have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

M.D.

Charles J. Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-142

UDL Laboratories, Inc,
U.S. Agent: Lachman Consultant Services, Inc.
Attention: Leon Lachman, Ph.D.
1600 Stewart Avenue
Westbury, NY 11590

MAY 12 1995

Dear Sir:

This is in reference to your abbreviated antibiotic application dated December 5, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Nystatin Oral Suspension, USP, 100,000 units/mL, 5 mL and 10 mL unit-dose cups.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

A. Chemistry Deficiencies

abeling Deficiencies:

ner (Unit Dose): 5 mL and 10 mL

Revise "NMT" to read: "...not more than...".

We find your proposed 10 mL unit-dose cup objectionable for the following reasons:

We note that the innovator does not have a 10 mL unit-dose package approved. The 5 mL is the only unit-dose package approved for this product. Your unit-dose package size must be the same as the innovator's.

In addition, "Unit-dose" packages imply a single dose and should be supported by the DOSAGE AND ADMINISTRATION section. The DOSAGE AND ADMINISTRATION section supports a usual single dose of 4-6 mL. Your proposed 10 mL unit-dose package exceeds that recommendation.

We recommend you ask for the withdrawal of the proposed 10 mL unit-dose package.

See comments under Container.

Relocate "10 Unit-Dose cups of 5 mL each" from the boxed area to another location. It appears too close to the strength of the product.

Please include the "Each mL" statement as described in the insert labeling (see comment 1.b. under Insert).

Revise the USUAL DOSAGE statement to read as follows:

USUAL DOSAGE: See package...

:e it

ıtibiotic

ws:

ntains
(not more
contains
...

)VERDOSAGE

:ord with

, with a

ılly well

ence.

reported
has been

:eptable.
:vise this

and insert
ıt (or

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

A request has been made through the Office of Compliance to arrange for pick-up of samples of your product for compendial testing.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be so designated in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

5/11/95

Frank O. Holcombe, Jr., Ph.D.
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-142

Lachman Consultant Services, Inc.
Agent for: UDL Laboratories, Inc.
Attention: Leon Lachman, Ph.D.
1600 Stewart Avenue
Westbury, NY 11590

JAN 11 1995

Dear Sir:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Nystatin Oral Suspension USP, 100,000 units/mL, 5 mL and 10 mL unit-dose cups

DATE OF APPLICATION: December 5, 1994

DATE OF RECEIPT: Decemeber 5, 1994

We will correspond with you further after we have completed the review of your application.

Please be advised that during the AADA approval process, samples of the active and inactive ingredients, and the AADA exhibit batch(es) (which should be the same as the biobatch if a bioequivalence study was conducted) may be collected by the FDA district office staff and tested by FDA district or headquarters laboratory staff. Drug substance standards and manufacturer's documentation of the impurity profile should be made available. In addition, batch records, certificates of analysis and specifications and tests for the drug substance, drug product and inactive ingredients may be collected.

The subject product of an AADA must conform to the current official compendial monograph requirements and be compatible with the test and assay methods described in that monograph. You must submit adequate documentation and laboratory data in your AADA that prove that any non-official alternate procedures that you choose to use for the analytical control (release) of your product are equivalent to the official compendial procedures. If this information is not submitted, the review of the application will be delayed.

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

Should you have questions concerning this application contact:

Mark Anderson

Consumer Safety Officer
(301) 594-0360

Sincerely yours,

1/11/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-142
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
HFD-473/Antimicrobial Drugs Branch
Endorsements: HFD-615/PRickman, Acting Chief 1/9/95 date
HFD-615/WRussell, CSO 1/9/95 date
HFD-643/JHarrison, Supervisory Chemist date 1/10/95
HFD-610/JPhillips,Chief, LRB 1/10/95
WP File\russell\60s\64-142
F/T by bcw/1-6-95
AADA Acknowledgement Letter!

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

December 5, 1994

ARCHIVAL COPY

Mr. Douglas Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: **Original Abbreviated Antibiotic Drug Application**
Nystatin Oral Suspension, USP
500,000 units/5 mL and 1,000,000 units/10 mL

Dear Mr. Sporn:

Pursuant to Section 507 of The Food, Drug and Cosmetic Act and 21 CFR 314.94 (c), we are herewith submitting an Abbreviated Antibiotic Drug Application for Nystatin Oral Suspension, USP. This Application is being submitted on behalf of UDL Laboratories, Inc. of Largo, Florida. A letter from UDL Laboratories, Inc. appointing Lachman Consultant Services, Inc. as their Agent immediately follows this cover letter.

In support of this Application, the information outlined below is provided:

- Table of Contents
- Application Form FDA 356h
- Basis for Submission
- Debarment, Convictions and Field Copy Certifications
- Comparison between the proposed drug and the reference listed drug (E.R. Squibb's Mycostatin®)

- Draft labels/labeling (four copies each in the archival [blue] and review [red] binders and one copy in the review [orange] binder)
- Request for a waiver of evidence of in vivo bioavailability as per 21 CFR 320.22
- Chemistry, manufacturing and controls information
- Methods validation package (one copy in the archival [blue] binder, one copy in the review [red] binder and two additional copies, each separately bound and identified in red binders)

The archival copy of this Application consists of three volumes.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Mary-Anne D'Esposito for

Leon Lachman, Ph.D.
President

Enclosure

83E4339