# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

# APPLICATION NUMBER:

# 64-195/S-003

| | |
|---|---|
| Generic Name: | Cyclosporine Oral Solution, USP (Modified) |
| Sponsor: | SangStat |
| Approval Date: | November 8, 1999 |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 64-195/S-003

**CONTENTS**

Reviews / Information Included in this ANDA Review.

| | |
|---|---|
| Approval Letter(s) | X |
| Tentative Approval Letter(s) | |
| Final Printed Labeling | |
| CSO Labeling Review(s) | |
| Medical Officer Review(s) | |
| Chemistry Review(s) | X |
| Microbiology Review(s) | |
| Bioequivalence Review(s) | |
| Administrative Document(s) | X |
| Correspondence | X |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 64-195/S-003

# APPROVAL LETTER

ANDA 64-195/S-003

SangStat
Attention: Eda S. Cook
1505 Adams Drive
Menlo Park, CA 94025

NOV 8 1999

Dear Madam:

This is in reference to your supplemental new drug application dated, January 28, 1999, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new drug application for Cyclosporine Oral Solution, USP (Modified) 100 mg/ml.

Reference is also made to your amendments dated July 30, 1999 and September 14, 1999.

The supplemental application provides for [redacted]

We have completed our review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our filed.

Sincerely Yours,

Vilayat Sayed 11/5/99

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 64-195/S-003

# CHEMISTRY REVIEW(S)

ANDA 64-195/S-003 CHEMIST REVIEW # 1

NAME AND ADDRESS OF APPLICANT:
Sangstat
1505 Adams Drive
Menlo Park, CA 94025

PURPOSE OF SUPPLEMENT
Provides for [redacted]

DATE OF SUBMISSION
January 28, 1999-- Original Submission

| PHARMACOLOGICAL CATEGORY | NONPROPRIETARY NAME |
|---|---|
| Antibiotic | Cyclosporine |

| DOSAGE FORM | POTENCY | RX OR OTC |
|---|---|---|
| Oral Solution | 100 mg/mL | Rx |

| SAMPLES | RELATED DMF | STERILIZATION |
|---|---|---|
| N/A | [redacted] | N/A |

LABELING
N/A

BIOEQUIVALENCY STATUS
N/C

ESTABLISHMENT INSPECTION
Will be issued by M. Anderson. Pending.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

[redacted]

form is included. A LOA to review DMF [redacted] and CGMP statement from [redacted] are included. ANDA [redacted] was approved on 10/31/97 and it was changed to DMF [redacted], on 11/3/98. No new updates have been filed with the DMF as of 6/8/99. DMF remain adequate.

[redacted] and firm's COAs for cyclosporine [redacted] lot

**Redacted** 4

**Page(s) of trade secret and /or confidential commercial information**

**ANDA** 64-195/S-003 **CHEMIST REVIEW # 2**

**NAME AND ADDRESS OF APPLICANT:**

Sangstat
1505 Adams Drive
Menlo Park, CA 94025

**PURPOSE OF AMENDMENT**

The amendment was submitted in reply to a deficiency letter dated July 2, 1999. The amendment provides:

1. FT-IR spectra for the bulk drug substance used in production of the demonstration lot and USP standard for comparison;

2. A table comparing the proposed [redacted] to the approved [redacted]

3. A comparative impurity profile presented in table form;

4. A stability study protocol proposing sampling intervals of 0, 3, 6, 9, 12, 18, 24, 36 months;

5. A commitment to place the first three commercial batches on stability study in accordance with the proposed protocol; and

6. A commitment to follow the approved stability protocol when generating data to extend the expiration date.

**PURPOSE OF SUPPLEMENT**

Provides for [redacted]

**DATE OF SUBMISSION**

Telephone Amendment: September 14, 1999
Amendment: July 30, 1999
Original Submission: January 28, 1999

| PHARMACOLOGICAL CATEGORY | NONPROPRIETARY NAME |
|---|---|
| Antibiotic | Cyclosporine |

| DOSAGE FORM | POTENCY | RX OR OTC |
|---|---|---|
| Oral Solution | 100 mg/mL | Rx |

| SAMPLES | RELATED DMF | STERILIZATION |
|---|---|---|
| N/A | [redacted] | N/A |

**LABELING**

N/A

**Redacted** 5

**Page(s) of trade secret and /or confidential commercial information**

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 64-195/S-003

# ADMINISTRATIVE DOCUMENTS

# FDA CDER EES
# ESTABLISHMENT EVALUATION REQUEST
# SUMMARY REPORT

Application: **ANDA 64195/003**
Stamp: **01-FEB-1999** Regulatory Due:
Applicant: **SANGSTAT**
**1505 ADAMS DR**
**MENLO PARK, CA 94025**

Priority:
Org Code: **600**
Action Goal:
District Goal: **01-JUL-1999**
Brand Name:
Established Name: **CYCLOSPORINE ORAL SOLUTION**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **100 MG/ML**

| FDA Contacts: | | | |
|---|---|---|---|
| **M. ANDERSON** | **(HFD-640)** | **301-827-5787** | **, Project Manager** |
| **J. CLARK** | **(HFD-800)** | **301-827-5918** | **, Review Chemist** |
| **R. ADAMS** | **(HFD-643)** | **301-827-5849** | **, Team Leader** |

Overall Recommendation:

**ACCEPTABLE on 22-OCT-1999 by M. EGAS (HFD-322) 301-594-0095**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CFN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER:

# 64-195/S-003

# CORRESPONDENCE

**SANGSTAT**
The Transplant Company®

September 14, 1999

via FedEx

Florence S. Fang
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, (HFD-641)
7500 Standish Place
Rockville, MD 20855

NDA SUPPL AMENDMENT
SC 003
Am 1

**ATTENTION: Mark Anderson, Consumer Safety Officer**

**RE: ANDA 64-195 / S-003**
**SangCya™ Oral Solution**
**(Cyclosporine Oral Solution, USP [MODIFIED]) 100 mg/mL**

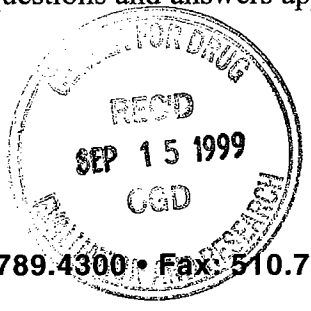
**MINOR TELEPHONE AMENDMENT**

Dear Ms. Fang:

We are submitting herewith, in triplicate, to the above referenced licensed product, a minor telephone amendment. This amendment is related to the supplemental application for [redacted].

The initial request, Chemistry, Manufacturing, and Controls Supplement to an Approved Application (S-003), was submitted on January 28, 1999. Subsequently, on July 2, 1999, this office responded that the supplemental application was deficient. On July 30, 1999, SangStat Medical Corporation (SangStat) responded to this letter. Then on August 19, 1999, Mr. Mark Anderson, Consumer Safety Officer, Office of Generic Drugs, contacted SangStat by telephone with two questions regarding another supplement application (S-001), for [redacted].

Subsequent to this telephone call, we have also reviewed the July 30, 1999, supplement filed to ANDA 64-195 / S-003. The same questions and answers apply to S-003.




6300 Dumbarton Circle • Fremont, CA 94555 • Tel: 510.789.4300 • Fax: 510.789.4400

The two questions are bolded and SangStat's responses follow:

1) **The Certificate of Analysis (C of A) for the cyclosporine drug substance required clarification. The chemistry reviewer noted the [redacted] was not listed as a specification on this C of A.**

We confirm the [redacted] test is performed. Eli Lilly (Lilly) reports the LOD result as "volatiles"; the result is listed on the C of A and reported as a percent. Attachment 1 contains a copy of page 2 from Lilly document QA 439N showing procedure B03436-001 which indicates LOD also known as volatiles.

2) **The Certificate of Analysis (C of A) for the final product required clarification. The chemistry reviewer noted "density" was not included as a specification on the C of A, which is not consistent with the specifications submitted in our August 14, 1997, major amendment response to the April 11, 1997, FDA chemistry review letter.**

At the time of the major amendment, the density measurement was being performed on final product as part of our development program and listed as a potential release specification. Subsequent to the amendment, it was later determined that this measurement is more relevant as a final bulk solution test before the solution is released for filling. Therefore, currently, the density measurement is being performed as an in-process test on final bulk solution. Since this test is performed as an in-process test, the results are not included on the final product C of A. The data for Lilly Lot Number D20706 are located in Attachment 2.

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.

Should you have any questions concerning the submitted information do not hesitate to contact me at (510) 789-4560 or facsimile at (510) 789-4205.

Sincerely,

Eda S. Cook
Senior Executive Director
Regulatory Affairs

**SANGSTAT**
The Transplant Company®

July 30, 1999

Ms. Florence S. Fang
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II (HFD-641)
7500 Standish Place
Rockville, Maryland 20855

SUPPL AMENDMENT
SC-003/Am.

**SUBJECT: SangCya™ Oral Solution**
**(Cyclosporine Oral Solution, USP [MODIFIED]), 100 mg/mL**
**ANDA # 64-195/S-003**

**MINOR AMENDMENT**

Dear Ms. Fang:

Reference is made to our supplemental new drug application dated January 28, 1999, submitted pursuant to 21 CFR 314.70, regarding our abbreviated new drug application for Cyclosporine Oral Solution, USP (**MODIFIED**), 100 mg/mL.

This supplemental application provided for [redacted]

This letter is in response to your correspondence dated July 2, 1999 in which you state our supplemental application is deficient and, therefore, not approvable under Section 505 of the Act. The following replies to your questions or statements, and provides the required attachments.

1. **Please provide comparative FT-IR spectra for lot no. 37270IL and a USP reference standard. Also, data comparing the physico-chemical properties of your approved and proposed cyclosporine USP raw material sources should be included.**

   Attachment 1 is the comparative FT-IR spectra for lot number 37270IL and a USP reference standard.

   Attachment 2 is a table with comparative data for the approved and proposed cyclosporine USP raw material. Spec table not test data

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 02 1999
OGD

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2. **Data from your comparative impurity profile study should be submitted in a table format for ease of review.**

   Attachment 3 is a table showing the data from the comparative impurity study.

3. **Regarding the post-approval stability protocol:**

   a. **The reduction of stability test intervals in your long-term stability protocol requires the submission of a prior approval supplemental application. Be aware that stability data for three commercial production batches should be included in the supplemental application for our review and approval prior to reduced testing intervals.**

      The deletion of the 3 and 9 month stations was noted. We will include 3 and 9 month time points in the post-approval study. We do not intend to reduce test intervals.

   b. **It is recommended that the first three commercial production lots be placed on long-term room temperature stability studies. Please revise and resubmit your post-approval stability protocol proposed prescribed test intervals to conform to the FDA Stability Guideline (i.e., 0, 3, 6, 9, 12, 18, 24, 36 months).**

      SangStat commits to place the first three lots of finished product made with [redacted] on stability.

      We will revise the proposed protocol for the lots made with [redacted] to conform to the FDA stability guideline. The protocol will specify test stations at 3, 6, 9, 12, 18, 24, and 36 months. The revised protocol is Attachment 4.

   c. **A post-approval commitment indicating how the expiration date of the finished drug product is extended should be provided. Please revise and resubmit your post-approval stability protocol.**

      SangStat commits to follow the approved stability protocol when generating data for date extension. Current data for batches on the stability program will be submitted as part of the annual report and dating will be extended when a minimum of three lots have reached the extended time point and have met the stability requirements.

4. Also included (in Attachment 5) is the current stability data for Eli Lilly Lot #D20706M using the [redacted]

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.

Pursuant to 21 CFR 314.70(a), a copy of this supplement has been sent to the applicant's home FDA district office in San Francisco, California.

If you should have any questions regarding the information in this submission, please do not hesitate to contact me by phone at (510) 789-4533, Colleen Stewart at (510) 789-4540, or by fax at (510) 789-4205.

Sincerely,

Mark Tolpin, M.D.
Senior Vice President
Clinical Research and Regulatory Affairs

Enclosure

ANDA 64-195/S-003

Sangstat
Attention: Colleen Stewart
1505 Adams Drive
Menlo Park, CA 94025

JUL -2 1999

Dear Madam:

This is in reference to your supplemental new drug application dated January 28, 1999, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug application for Cylosporine Oral Solution, USP (modified) 100 mg/mL.

The supplemental application provides for [redacted]

The supplemental application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Please provide comparative FT-IR spectra for lot no. 37270IL and a USP reference standard. Also, data comparing the physico-chemical properties of your approved and proposed cylosporine USP raw material sources should be included.

2. Data from your comparative impurity profile study should be submitted in a table format for ease of review.

3. Regarding the post-approval stability protocol:

   a. The reduction of stability test intervals in your long-term stability protocol requires the submission of a prior approval supplemental application. Be aware that stability data for three commercial production batches should be included in the supplemental application for our

review and approval prior to reducing testing intervals.

b. It is recommended that the first three commercial production lots be placed on long-term room temperature stability studies. Please revise and resubmit your post-approval stability protocol proposed prescribed test intervals to conform to the FDA Stability Guideline (i.e., 0, 3, 6, 9, 12, 18, 24, 36 months).

c. A post-approval commitment indicating how the expiration date of the finished drug product is extended should be provided. Please revise and resubmit your post-approval stability protocol.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this supplemental 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. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reason for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

R.C. Adams for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

**SANGSTAT**
The Transplant Company®

EER to be requested
M Anderson 2/12/99

January 28, 1999

ARCHIVAL COPY

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

NDA NO. 64195 REF. NO. SC-003
NDA SUPPL FOR Facility Addition

**SUBJECT: SangCya™ Oral Solution**
**(Cyclosporine Oral Solution, USP [MODIFIED]), 100 mg/mL**
**ANDA # 64-195**

**CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT TO AN APPROVED APPLICATION**

Dear Mr. Sporn:

Reference is made to the subject original abbreviated new drug application (ANDA), and to the agency's approval letter for that application dated October 31, 1998. Pursuant to 21 CFR 314.70 (b)(1)(v), we herewith submit a supplement to use [redacted] Specifically, SangStat Medical Corporation is proposing to add [redacted]

Contract manufacturer Eli Lilly and Company manufactured a [redacted] test batch (Lot number D20706M) of SangCya™ Oral Solution (Cyclosporine Oral Solution, USP [MODIFIED]), 100 mg/mL, containing drug substance manufactured by Abbott Laboratories. Documentation supporting the executed batch record for Lot number D20706M is enclosed. Specifically, the executed batch record for the test batch is provided in Attachment 3. As noted in Attachments 2 and 4, the test batch was tested in accordance with the previously approved ANDA commitments and procedures, and placed on stability under accelerated and controlled room temperature conditions (Attachment 5). All specifications were met.

RECEIVED
FEB 0 1 1999

1505 Adams Drive • Menlo Park, CA 94025 • Tel: 650.328.0300 • Fax: 650.328.8892

Recognizing that alternate manufacturers of the same drug substance typically utilize a different process or synthetic route, the impurity profiles are often different. In this case, the [redacted] process introduced the need to analyze for a residual solvent [redacted]. Accordingly, we have revised the SangStat drug substance specifications with limits for [redacted] and added a test method (USP XXIII) for the analysis of [redacted].

The excipients are identical to and have the same specifications and limits as those present in the approved ANDA # 64-195 (10/31/98). Additionally, the finished drug product, made with the material [redacted] from [redacted]

- Has the same stability profile (data from the exhibit batch Lot D20706M stored accelerated conditions and at the room temperature)
- Has comparable impurity profiles
- Meets all finished drug specifications approved for ANDA # 64-195
- Has the same physico-chemical parameters as the drug product approved for ANDA # 64-195

In summary, we have enclosed the following in support of this supplement:

- Index / Table of Contents.
- Application Form FDA 356h and third copy field certification.
- Letter from [redacted] authorizing FDA to access [redacted] AADA # 64-208.
- cGMP certification letter from [redacted]
- SangStat Revised Drug Substance specifications to include analysis for residual solvent hexane.
- Contract Manufacturer's Eli Lilly's results for [redacted] lot no. 37270IL00 (Eli Lilly lot no.C80003), including spectra and chromatograms for standards and samples.
- Executed batch records (manufacturing and packaging) for a [redacted] batch (lot number D20706M) of SangCya™ Cyclosporine Oral Solution, USP [Modified], 100 mg/mL, containing drug substance lot 37270IL00, manufactured at [redacted]
- SangStat's test results/ Eli Lilly Certificate of Analysis for exhibit batch lot number D20706M
- SangStat's Stability Summary Data for exhibit batch lot number D20706M
- Stability Commitment addendum reflecting firm's commitment to place the first commercial production batch containing drug substance manufactured by [redacted] on stability under controlled room temperature conditions.

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.

Pursuant to 21 CFR 314.70(a), a copy of this supplement has been sent to the applicant's home FDA district office in San Francisco, California.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned by phone [(650) 688-2335] or by fax [(650) 853-1256].

Sincerely,

Hana Berger Moran

Hana Berger Moran, Ph.D.
Sr. Vice President
Regulatory Affairs and Quality Assurance

Enclosure: January 28, 1999 *Supplement to **ANDA # 64-195**- SangCya*™ Oral Solution, (Cyclosporine Oral Solution, USP [Modified]), *100 mg/mL*