

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER 64195**

**ADMINISTRATIVE DOCUMENTS**

ANDA APPROVAL SUMMARY

ANDA: 64-195 DRUG PRODUCT: Cyclosporine Oral Solution for  
Microdispersion

FIRM: SangStat DOSAGE FORM: oral solution STRENGTH: 100 mg/mL

CGMP STATEMENT/EIR UPDATE STATUS: **Acceptable 7/23/98**

BIO STUDY: Satisfactory

Bioequivalence information found complete by Moo Park in the  
review dated January 20, 1998.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Satisfactory

SangStat submitted samples with COAs for testing to:

Food and Drug Administration

Beltsville Research Facility

Attention: Valerie Flourney (HFD-910)

8501 Muirkirk Road

Laurel, MD 20708

(Telephone: 301-827-8054)

The test results are acceptable dated October, 1997.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN  
CONTAINER SECTION?): Satisfactory

The containers used in stability are the ones specified in the  
application.

Expiration dating: 24 months based on 3 months accelerated  
stability data (

Stability Specifications:

can.

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Stability Data:

Data is provided for a completed 3 month accelerated  
stability study. The data reports indicate the product is  
within specifications throughout the study.

Partial data is provided for 24 months long term stability data . The data reports indicate the product is within specifications so far.

LABELING: **Acceptable 10/7/98**

STERILIZATION VALIDATION (IF APPLICABLE): N/A

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

Exhibit batch: Executed batch records for a batch are provided, lot # D20571

Manufacturing batch size:  
Exhibit batch size:

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

The bio batch is used for the stability studies.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

The production method is the same as the exhibit batch method.

CHEMIST:

/S/

10-20-78

DATE:

SUPERVISOR:

DATE:

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: August 6, 1997

FROM: Jerry Phillips *Jerry Phillips*  
Director, Division of Labeling and Program Support

THRU: Frank Holcombe  
Director, Division of Chemistry II

SUBJECT: Determination whether AADA 64-195 meets definition of a  
Microemulsion

TO: John Clark

During a teleconference with \_\_\_\_\_ and \_\_\_\_\_ (of \_\_\_\_\_) the applicant's (Sangstat) chemist believe that their formulation is NOT a microemulsion. They believe that oil, which is NOT present in their formulation, is an essential component for a microemulsion. They have defined their Cyclosporin Oral Solution as a Microdispersion of solid tiny particles (or nanoparticles) of cyclosporin. The firm is requesting a determination be made now that would include a consensus by NDE and OGD that their formulation is acceptable to be labeled "Cyclosporin Oral Solution for Microemulsion". They would like to propose to label their solution differently than the RLD, since they don't believe they meet the definition.

I have included definitions of a microemulsion from Remington and the USP. From my observation of the definitions, oil does seem to be an essential component. In addition, the immiscibility of the oil with water is mentioned. Both \_\_\_\_\_ and \_\_\_\_\_ present in the formulation for SangStat is \_\_\_\_\_ MISCIBLE in water.

The approvability of this AADA could be tied to this issue, so I am requesting that a formal determination be made as soon as possible. Any communication with NDE should be clarified that this is sensitive and confidential information about an unapproved application and must not be shared with the innovator firm. In addition, if a meeting is arranged with NDE to discuss this please include myself, Gordon, and Don Hare in the discussion. Thanks for your assistance!

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

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ANDA Number: 64-195

Date of Submission: March 3, 1998 and March 9, 1998

Applicant's Name: SangStat Medical Corporation

Proposed Established Name: Cyclosporine Oral Solution for  
Microdispersion, 100 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. We have forwarded your proprietary names SangCya™, Cycloprine™ and to the Labeling and Nomenclature Committee for their review and comment. We will inform you of their response as soon as it becomes available.
- b. We acknowledge your comment regarding the established name of this drug product.

2. CONTAINER

We note you have not submitted revised container labels. Please submit for our review.

3. CARTON

- a. Increase the prominence of "**for Microdispersion**" where it appears throughout your carton labeling.
- b. BOXED WARNING  
Print "**WARNING**" in bold uppercase print.
- c. We note that the reference listed drug has listed the alcohol content in terms of percent volume/volume followed by (weight/volume) in parentheses. Please revise to be consistent with the reference listed drug throughout your carton

labeling.

d. Front panel

Replace the "R Only" with "R only".  
[Note: lowercase "o"].

e. Back Panel

i. Revise as follows:

The precision "pump" allows accurate dosing,  
less waste and less mess. Do not rinse ...

ii. Item 1

We note that the reference listed drug  
includes instructions to "remove rubber  
stopper and discard" after the flip-up cap  
has been opened and the aluminum seal has  
been removed. Does your product contain a  
rubber stopper that should be discarded prior  
to the attachment of the clear stopper?  
Please comment.

iii. Item number 5

Revise to read, "... bottle. Reseal bottle  
...".

4. INSERT

a. General Comments

i. Replace the "R Only" with "R only".  
[Note, lowercase "o"].

ii. When referring to "Sandimmune®" use the  
established name "Cyclosporine Oral  
Solution". Revise accordingly throughout the  
text of the insert labeling.

iii. When expressing a range of percentages,  
revise to read as "4% to 9%" instead of  
"4-9%". Revise accordingly throughout the  
text of the insert labeling.

iv. Delete the terminal zero following a decimal  
point, i.e., "4" instead of "4.0". Revise  
accordingly throughout the text of the insert

labeling.

v. Revise your paragraph breaks to be the same as the reference listed drug.

vi. There are sections of the insert labeling where you must delete reference to your specific drug product. Note, studies that were not conducted with your drug product should read "cyclosporine for microemulsion". Revise accordingly throughout the text of the insert labeling. ✓

vii. Revise the format of your subsection and subsection headings to be consistent throughout the text of your labeling.

viii. We note you have omitted, as well as, added text throughout your insert labeling that differs from the reference listed drug, in some cases without explanation in your annotated side-by-side submission. For the comments that follow, we request that you submit an explanation regarding the altered text and/or revise to read the same as the reference listed drug. We also refer you to 21 CFR 314.94(a)(8)(iv).

b. Boxed WARNINGS

i. Second box

Revise as follows:

A) Cyclosporine capsules for microemulsion, cyclosporine oral solution for microemulsion and cyclosporine oral solution for microdispersion have increased bioavailability in comparison to cyclosporine capsules and cyclosporine oral solution. Cyclosporine oral solution for microemulsion/cyclosporine oral solution for microdispersion and cyclosporine oral solution are not bioequivalent and cannot ... supervision. For a given trough ... greater with cyclosporine oral solution for microemulsion/cyclosporine oral solution for microdispersion than with cyclosporine oral solution. If a ✓

patient ...

- B) Revise the third sentence to read as follows:

...in transplant and rheumatoid arthritis patients taking ...

- ii. Third box

Revise the following text to appear in bold and italic print:

**For Psoriasis patients (See also Boxed WARNINGS above)**

c. DESCRIPTION

- i. We note that the reference listed drug has listed the alcohol content in terms of percent volume/volume followed by percent (weight/volume) in parentheses. Please revise to be consistent with the reference listed drug.

- ii. Fourth paragraph

We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this drug product. An incidental trace ingredient having no functional or technical effect on the product need not be listed unless it has been demonstrated to cause sensitivity reactions or allergic response (i.e., dyes). An inactive ingredient need not be listed if it is deemed a trade secret. If you elect not to mention an inactive ingredient because it is a trade secret, you can use the phrase "and other ingredients", and provide supporting data concerning the 'trade secret'. We also refer you to 21 CFR 201.10.

iii. Last paragraph

Revise "chemical structure" to read "structural formula".

iv. Revise the structural formula to consistent with the reference listed drug.

v. Revise the molecular weight to be consistent with USP 23, 1202.64.

vi. We note that in your side-by-side submission you have indicated the following:

"Delete sentence because proposed product does not form a true Microdispersion."

Please comment.

d. CLINICAL PHARMACOLOGY

i. See General Comment 4(a)(vi).

ii. Pharmacokinetics

In the last paragraph revise "SangCya™" to read "cyclosporine oral solution for microemulsion".

iii. Absorption

Revise the first paragraph to read as follows:

A) ... of cyclosporine administered as ...

B) Revise the second paragraph to read as follows and/or comment:

... from 1.5 to 2 hours. The administration of ... decreases the cyclosporine AUC and  $C_{max}$ .

C) Table

Revise the table to read as follows and/or comment:

- In the first row relocate each

superscript to appear at the end of the text heading instead of at the beginning of the text heading, [i.e., "De novo renal transplant"<sup>4</sup> instead of "<sup>4</sup>De novo renal transplant"].

- Pharmacokinetic Parameters (mean±SD) [Delete "in Adult Patients"].
- Revise the numerical superscripts to read the same as the approved insert labeling of the reference listed drug, Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: revised June 18, 1997 and approved June 19, 1997, which was sent to your firm with the labeling deficiencies from your submission dated August 22, 1997 and/or comment.
- Print "De novo" in italic print. [Note: three locations]
- Correct numerical values listed in the last two columns for, "De novo rheumatoid arthritis<sup>6</sup> (N=23)".

#### iv. Special Populations

##### A) Pediatric Population

- Revise the first sentence to read as follows:  
  
Pharmacokinetic data from pediatric patients administered cyclosporine oral solution for microemulsion or cyclosporine oral solution are very limited. In ...
- Revise "Cyclotrac" to read "Cyclo-trac" in the first paragraph and delete the semicolon.
- Revise the second paragraph to read as follows:

In the pediatric population cyclosporine oral solution for microemulsion also demonstrates an increased bioavailability as compared to cyclosporine oral solution.

- Table

In the first row relocate each superscript to appear at the end of the text heading instead of at the beginning of the text heading, [i.e., "Stable liver transplant<sup>2</sup>" instead of "<sup>2</sup>Stable liver transplant"].

e. CLINICAL TRIALS (Rheumatoid Arthritis)

i. Throughout this section replace "Sandimmune®" with "cyclosporine oral solution" and "SangCya™" with "cyclosporine oral solution for microemulsion".

ii. Second paragraph

Print "completed" in italic print.

iii. Third paragraph

Revise as follows:

...three groups: (1) cyclosporine dosed at 2.5 to 5 mg/kg/day, (2) methotrexate...

iv. Revise the last paragraph to read as follows:

A) ... were started at 2.5 mg/kg/day and increased ...

B) ... 5 mg/kg/day and decreased at any time for toxicity.

C) Graph

We note you have omitted portions of the graph. Revise the graph to read the same as it appears in the approved labeling of the reference listed drug,

Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: revised June 18, 1997 and approved June 19, 1997, which was sent to your firm with the labeling deficiencies from your submission dated August 22, 1997. In addition, improve the readability of the entire graph.

f. WARNINGS

- i. Revise the section heading to appear as follows:

**WARNINGS** (See also Boxed WARNING)

ii. All Patients

- A) Print the last sentence of the first paragraph in bold print, "Care ... drugs. (See PRECAUTIONS)."
- B) Print the text, "(See Special Monitoring under ...)" in italic print.
- C) Because cyclosporine oral solution for microdispersion and cyclosporine oral solution for microemulsion are not bioequivalent to cyclosporine oral solution, conversion from cyclosporine oral solution for microdispersion to cyclosporine oral solution using...Conversion from cyclosporine oral solution for microdispersion to cyclosporine oral solution... ✓

iii. Kidney, Liver, and Heart Transplant

Nephrotoxicity vs. Rejection (Chart)

- Revise so that the text of the columns and rows coincide, as seen in the reference listed drug.
- In the row "History" and beneath the column "Rejection", revise "Antidonor" to read "Anti-donor".

- In the row "Aspiration Cytology" and beneath the column "Rejection", revise "Iymphoblastoid" to read "lymphoblastoid".

iv. Rheumatoid Arthritis

Revise the first paragraph to read, "... with a dose  $\leq$ 4 mg/kg/day. Serum creatinine improved ...".

v. Psoriasis

In the third paragraph print the text, "(See *Special Monitoring under ...*" in italic print.

g. PRECAUTIONS

i. General

A) Hypertension

Revise this subsection to read same as that of the reference listed drug, Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: revised June 18, 1997 and approved June 19, 1997, which was sent to your firm with the labeling deficiencies from your submission dated August 22, 1997 and/or comment.

B) Special Monitoring of Rheumatoid Arthritis Patients

Revise the last sentence of the first paragraph to read as follows:

... monthly. (See also *PRECAUTIONS, General, Hypertension*).

C) Special Monitoring for Psoriasis Patients

- Print the subsection heading "*Special Monitoring for Psoriasis Patients*" in italic print to be consistent with your other sub-

subsection headings.

- In the last sentence of the first paragraph, remove the inappropriate period appearing in the middle of sentence, [... only after ...].

- Revise the fourth paragraph as follows:

If at **any time** the serum ...  
[Note bold print].

- In the fourth sentence of the fourth paragraph, remove the inappropriate period appearing in the middle of sentence, [... should be reduced ...].

#### D) Drug Interactions

- We note the appearance/format of your sub-subsection headings under the subsection heading "Drug Interactions" are not consistent.
- Print this subsection in italic print. In addition, print the text in the same format as the reference listed drug including the italic print where it appears.
- *Methotrexate Interaction*  
... have been altered (N=6).
- *Other Drug Interactions*
  - Start a new paragraph with the sentence, "During treatment with ...".
  - Delete the text, "Further information on drugs that have been reported to interact with cyclosporine is available from SangStat Medical Corporation".

E) Carcinogenesis, Mutagenesis, and Impairment of Fertility

Let the last sentence in the second paragraph start a new paragraph, "No impairment in ... rats".

F) Pregnancy

- First paragraph

- ... test systems. Only at dose levels toxic to ...
- ... 5.4 times the transplant doses in humans 6 mg/kg, ...

- Third paragraph

- ... pregnancy, 90% of ...  
[comma instead of period]
- "Pre-term" instead of "Preterm".

G) Pediatric Use

Revise "children" to read "pediatric patients".

h. ADVERSE REACTIONS

i. See comment 4(vi) under GENERAL COMMENTS.

ii. Revise this section to be in accord with the attached insert labeling of the reference listed Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: acknowledge and retained on November 20, 1997 and revised June 1997.

iii. Fifth paragraph

Revise as follows:

In controlled studies, the ... treated with cyclosporine oral solution for microemulsion were comparable ... who received cyclosporine oral solution in these same studies ...

i. OVERDOSAGE

Revise the last sentence to read as follows:

... maintenance dose for transplant patients  
(6 mg/kg; corrections ...

j. DOSAGE AND ADMINISTRATION

i. Revise the first paragraph to read as follows:

- Delete the duplicate text appearing in the first paragraph.

- Cyclosporine oral solution for microemulsion has increased bioavailability in comparison to cyclosporine oral solution. Cyclosporine oral solution for microemulsion and cyclosporine oral solution for microdispersion are not bioequivalent to cyclosporine oral solution and cannot...

ii. Newly Transplanted Patients

Revise to read as follows:

... blood concentration. (See Blood Concentration . . .

iii. Revise the second subsection to read as follows and/or comment:

- **Conversion from ... in Transplant Patients**

- ... dosing strategies. (See Transplant Patients with Poor Absorption ...

iv. Psoriasis

- Revise the second paragraph to read as follows:

... creatinine ( $\geq 25\%$  above the ...

- Revise the penultimate paragraph to read as follows:

... below 2.5 mg/kg/day may also...

v. Blood Concentration Monitoring in Transplant Patients

Revise the last paragraph to read the same as that appearing in the labeling of the reference listed drug, Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: revised June 18, 1997 and approved June 19, 1997, which was sent to your firm with the labeling deficiencies from your submission dated August 22, 1997 and/or comment.

k. HOW SUPPLIED

i. Indicate that your 50 mL bottles are packaged individually.

ii. Store and Dispense

Revise to read the same as that appearing in the labeling of the reference listed drug, Neoral® (Cyclosporine Oral Solution for Microemulsion) by Novartis Pharmaceutical Corporation: revised June 18, 1997 and approved June 19, 1997, which was sent to your firm with the labeling deficiencies from your submission dated August 22, 1997 and/or comment.

iii. We encourage the inclusion of the "Rx only" in this section.

Please revise your labels and labeling, as instructed above, and submit in draft.

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

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

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

Attachment: Neoral® ADVERSE REACTIONS section from the insert labeling

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