CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64195

CORRESPONDENCE

SangStat Medical Corporation
The Transplant Company®

August 14, 1997

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Subject: **AADA # 64-195 SangStat COSM**
Cyclosporine Oral Solution for Microemulsion, 100 mg/mL
Response to Bioequivalence Comment Letter Dated May 20, 1997

Dear Sirs:

This amendment is being submitted in response to the Office of Generic Drugs' letter dated May 20, 1997. This letter transmitted comments regarding the bioequivalence review portion of our AADA for Cyclosporine Oral Solution for Microemulsion, 100 mg/mL.

SangStat has responded to each of the reviewer's comments. For ease of review, the reviewer's comments are reproduced in italics with the SangStat's response immediately following the respective comment. In addition, a copy of the Agency's May 20, 1997, correspondence is attached immediately after the Form FDA 356h (revised 4/97).

We respectfully request that this information is treated as confidential. We hope that the enclosed responses satisfactorily address your comments. Should you have additional questions, please contact me at (415) 688-2335.

Sincerely yours,

Hana B. Moran

Hana B. Moran, PhD
Senior Vice President
Regulatory Affairs and Quality Assurance

Enclosures

1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

Comment 1. *The following are in reference to both bioequivalence studies, # 18327 conducted under fasting conditions and the food effects study # 18328:*

1.a. It is unclear exactly how the standard curves were calculated using the Abbott TDx system software. Supply an example of the calculation of a typical standard curve, starting from the raw data. An example should also be furnished of the assay calculations for a typical unknown sample, based on this standard curve.

Page(s) 8

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Comments 3.c

The actual subject blood collection times for the 0.5 hour time point differed significantly from the scheduled time. The report states that the actual times were used to compute the AUC's, but an analysis by the Division of Bioequivalence indicated that the theoretical times were used. Please rectify this apparent discrepancy.

Response 3. c.

The discrepancy in the blood collection of the 0.5 hr samples was an error which was discovered at the time of the collection. Immediately after notification from the clinical site this fact was discussed with Dr. Keith Chan and Dr. Jason Gross of the Division of Bioequivalence, OGD.

The recommendation was to note the time of the collection and continue as planned for the remainder of the timepoints. A deviation report was also prepared by ies and included in the final study report. The letter from SangStat and the subsequent teleconference report is attached (Attachment XI.).

The recalculation of the study data using the actual collection times of the blood collection is also presented (Attachment XII). The data following recalculation had provided the same outcomes of the pharmacokinetic parameters, that determined the bioequivalence, i.e. AUCs and C_{max},. The other PK parameters also remained unchanged.

SangStat Medical Corporation
1505-B Adams Drive
Menlo Park, California 94025
Telephone: (415) 328-0300
FAX: (415) 328-8892

June 10, 1997

Food and Drug Administration
Center for Devices and Radiological Health
Division of Dental, Infection Control,
and General Hospital Devices
Office of Device Evaluation
9200 Corporate Blvd.
Rockville, MD 20850

Attention: **Ms. Pat Cricenti, Acting Branch Chief**
General Hospital Devices Branch

Page(s) 4

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Device

John Harrison

SangStat Medical Corporation
The Transplant Company®

August 6, 1997

Food and Drug Administration
Center for Devices and Radiological Health
Division of Dental, Infection Control,
and General Hospital Devices
Office of Device Evaluation
9200 Corporate Blvd.
Rockville, MD 20850

Attention: **Ms. Pat Cricenti, Acting Branch Chief**
General Hospital Devices Branch

SangStat Medical Corporation
The Transplant Company®

ORIG AMENDMENT
N/A M

30 June 1998

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

MINOR TELEPHONE AMENDMENT
Contains chemistry and labeling comments

Subject: **ANDA #64-195, SangCya™,**
Cyclosporine Oral Solution for Microdispersion, 100 mg/mL

Dear Mr. Sporn

Reference is made to our abbreviated new drug application dated November 21, 1996 for Cyclosporine Oral Solution for Microdispersion, 100 mg/mL.

Please refer to your June 23, 1998, Minor Telephone Amendment fax (chemistry and labeling) responding to SangStat Medical Corporation's Minor Amendment submissions dated March 3, and March 9, 1998, containing responses to OGD chemistry and labeling comments outlined in your letter of February 4, 1998.

This communication addresses the current chemistry and labeling issues raised in the above referenced fax of June 23, 1998.

Also, please refer to the June 30, 1998, telephone conversation between Dr. Jacqueline White, OGD, Division of Labeling and Program Support and Hana B. Moran, Ph.D., SangStat. Two comments from the June 23, 1998, OGD letter to SangStat were discussed. One addressed a comment requesting us to use "cyclosporine for microemulsion" when referring to innovator's product to utilize the established name of the innovator to read "cyclosporine oral solution for microemulsion". This request was found appropriate and acceptable to Dr. White.

The second issue was the requested revision of the text in *Boxed WARNINGS* as noted in the OGD Letter of June 23, 1998. OGD Requested SangStat utilize the statement "Cyclosporine oral

solution for microemulsion / cyclosporine oral solution for microdispersion and cyclosporine oral solution are not bioequivalent and cannot.....". This statement may be confusing to the physicians and the pharmacists as it could imply that all three products are not bioequivalent.. Therefore we would like to recommend the adoption of the following: "Cyclosporine oral solution for microemulsion and cyclosporine oral solution for microdispersion are bioequivalent, however, they are not bioequivalent to cyclosporine oral solution and cannot be used ....." . Dr. White recommended that SangStat include this proposed statement in the draft Package Insert for review and consideration.

We also wish to comment on your request to list the inactive ingredients in the package insert. It is imperative for SangStat that it maintains the identities and the proportions of the "inactive ingredients" of SangCya™ as a trade secret. The proportions and identities of these "inactive ingredients" are essential to the overall bioequivalence of SangCya to cyclosporine oral solution for microemulsion. Any disclosure of these "inactive ingredients" by identity or proportion will potentially harm SangStat's competitive position in the marketplace. Disclosure may enable competitors to gain an unfair advantage in the Cyclosporine marketplace based on SangStat's extensive research and development activities on SangCya.

There are no inactive ingredients in the SangStat product that should or could pose a public health issue. None of the ingredients that we are not listing as trade secret, cause allergic type reactions, cause sensitivity or are of the type that would, according to our review of the literature pose a threat to the health of patient if not disclosed.

As an alternative and in accordance with your recommendation we prefer to use phrase "and other ingredients" in the description section of the package insert and in the labeling.

SangStat is amending its application to respond all issues raised in your fax. The response is formatted in the following manner: the FDA question or comment is repeated (in italics) followed by the SangStat response written in normal font. The reviewer will be directed to the appropriate attachment (if additional information, beyond the narrative, is required to address your comments).

A complete copy of this response is also being provided to the FDA District Office, Alameda, CA in accordance with the regulations promulgated in 21 CFR Part 314.96(b). A copy of the cover letter is included here.

SangStat requests 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 released to an applicant without written consent by SangStat to an authorized member of your Office.

If you have any questions, please contact me by telephone at (650) 688-2335 or by fax at (650) 853-1256.

Sincerely,

Hana Berger Moran

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

Enclosures

cc: Mr. R. Johnson, FDA District Office, Alameda, California

Philippe Pouletty, M.D.

ANDA 64-195

DRUG PRODUCT: Cyclosporine Oral Solution (for Microdispersion), 100 mg/mL

The following deficiencies were identified based on the chemistry review of your May 12, 1998 amendment:

Deficiencies:

Please revise the release and stability specifications for It currently reads: v/v of labeled amount. The term "of labeled amount" is confusing and should be stricken from the specification.

Please provide the calculated results of testing the innovator product according to the methodology and reporting method described in the regulatory "Related substances" specifications. These results should be provided with the results from the analysis of the SangStat product for side by side comparison.

Please reinstate the previously submitted stability and release specifications for density and the release specification for deliverable volume.

Your response should be submitted to the application as a hard copy with a signed Form 356h as a "TELEPHONE MINOR AMENDMENT". A fax copy of the cover letter may be sent to 301-443-3839.

SangStat Medical Corporation
The Transplant Company™

ORIG AMENDMENT
N/Amy

May 12, 1998

Mr. Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

MINOR TELEPHONE AMENDMENT

Subject: **ANDA #64-195, SangCya™,**
brand of Cyclosporine Oral Solution for Microdispersion, 100mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated November 21, 1996, Cyclosporine Oral Solution for Microdispersion.

Reference is also made to your April 14, 1998, fax of a Minor Telephone Amendment comments to the March 3, 1998, SangStat responses to February 4, 1998, Minor Amendment letter. Also, please refer to the May 7, 1998, telephone conversation between John Harrison, Supervisory Chemist, OGD and Hana B. Moran, of SangStat. A brief summary of that conversation is incorporated into SangStat response # 3 of this submission.

SangStat is amending its application to respond to all of the issues raised in your fax. The response is formatted in the following manner: The FDA question or comment is repeated (in italics) followed by the narrative of the SangStat response. The reviewer will be referred to the appropriate exhibit in attachment if additional information beyond the narrative is required to address the agency's concern.

The responses address the chemistry issues. We understand that the labeling review is ongoing

A complete copy of this response is also being provided to the FDA District Office, Alameda, CA in accordance with the regulations promulgated in 21 CFR Part 314.96(b). A copy of the cover letter is included here.

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MAY 14 1998
GENERIC DRUGS

1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

Madhu

SangStat requests 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 released to an applicant without written consent by SangStat to an authorized member of your Office.

If you have any immediate objection or questions, please contact me by phone at (650) 688-2335 or by fax at (650) 853-1256.

Sincerely,

Hana Berger Moran

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

cc: Philippe Pouletty, M.D.

ANDA 64-195
DRUG PRODUCT: Cyclosporine Oral Solution

The following deficiencies were identified based on the chemistry review of your March 3, 1998 submission:

Deficiencies:

1. The list of stability specifications and the list of release specifications that you provided are deficient as follows:

   a. Both of the lists have deleted the particle size specification for the product after it is mixed with water. Please reinstate this testing specification for both product release and for stability. In addition, please provide particle size data for a sample that has completed 3 months accelerated stability or 24 months long term stability and was then mixed with water.

   b. The impurity limit specifications were deleted from the stability specifications. Please revise the stability specifications to include limit specifications on impurities. The allowable limits for impurities are discussed later in this letter.

2. You provided stability data for a sample that has completed 22 months under long term stability conditions and you adjusted the expiration dating to 18 months accordingly. Particle size data are not provided for a sample that was mixed with water after completing the stability study. Please provide these data.

3. You lowered the limit specification for impurities so that the sum of the "total known" and the "total unknown" is . The stability data indicate that the samples meet the requested limit of Please lower the specification or, alternatively, provide a direct comparison of your product with the innovator product using the SangStat testing methodology.

Please submit your response (hard copy) with a signed Form 356h as a "MINOR TELEPHONE AMENDMENT" to the application. A fax copy may be sent to 301-443-3939.

SangStat Medical Corporation
The Transplant Company™

March 3, 1998

ORIG AMENDMENT
N/AM

Mr. Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

MINOR AMENDMENT

Subject: **ANDA #64-195, SangCya™,**
brand of Cyclosporine Oral Solution for Microdispersion, 100mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated November 21, 1996, Cyclosporine Oral Solution for Microdispersion.

Reference is also made to your February 4, 1998, fax transmitting comments and deficiencies in regard to the chemistry and labeling review of our ANDA and amendments of August 22, and 29, 1997. Your fax indicated that SangStat's response will be considered as a minor amendment.

SangStat is amending its application to respond to all of the issues raised in your letter. The response is formatted in the following manner: the FDA question or comment will be reproduced (in italics) followed by the narrative of the SangStat response. The reviewer will be referred to the appropriate exhibit/appendix if additional information beyond the narrative is required to address the agency's concern.

The responses address the chemistry issues followed by the labeling issues. In addition to the labeling comments and revisions requested in your February 4, 1998, fax, SangStat has revised the "Caution: Federal law prohibits dispensing without prescription" statement to "Rx only", in accordance with section 126 of the Food and Drug Administration Modernization Act (FDAMA) of 1997. This change has been made to the product label, carton label and insert labeling.

In addition this amendment proposes a new proprietary name for the proprietary product. SangStat has also proposed two alternate proprietary names in the event the agency is not satisfied with our primary preferred name SangCya™.

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1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

Madeline 3-5-98

SangStat acknowledges that the Division of Bioequivalence has completed its review and has no further questions at this time.

A complete copy of this response is also being provided to the FDA District Office, Alameda, CA in accordance with the regulations promulgated in 21 CFR Part 314.96(b). A copy of the cover letter is included here.

SangStat requests 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 released to an applicant without written consent by SangStat to an authorized member of your Office.

If you have any immediate objection or questions, please contact me by phone at (650) 688-2335 or by fax at (650) 853-1256.

Sincerely,

Hana Berger Moran

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

cc: Philippe Pouletty, M.D.

SangStat Medical Corporation
The Transplant Company™

August 22, 1997

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AF

Subject: **Labeling Amendment AADA # 64-195**
SangStat COSM, Cyclosporine Oral Solution for Microemulsion 100 mg/mL

Dear Sirs:

This amendment is being submitted in response to the Office of Generic Drugs' letter dated April 11, 1997. This letter transmitted comments of the Division of Labeling and Program Support, OGD, regarding the labeling review portion of the AADA # 64-195 for SangStat COSM, Cyclosporine Oral Solution for Microemulsion, 100 mg/mL (SangStat COSM).

SangStat has responded to each of the reviewer's comments. However, as pertaining to *Comment 4. Insert*, SangStat was unable at this time to obtain the most current approved labeling for the innovator product. This most current approved labeling would contain also the indications for rheumatoid arthritis and psoriasis. As soon as SangStat obtains these labels it will submit the amended insert to the OGD in a draft form. All other reviewer comments were implemented. In the meantime we respectfully request that the amended draft labeling be reviewed. A copy of the Agency's April 11, 1997, correspondence is attached immediately after the Form FDA 356h (revision 4/97).

We respectfully request that this information is treated as confidential. We hope that the enclosed responses satisfactorily address your comments. Should you have additional questions, please contact me at (415) 688-2335.

Sincerely yours,

Hana B. Moran

Hana B. Moran, PhD
Senior Vice President
Regulatory Affairs and Quality Assurance

Enclosures

1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

SangStat Medical Corporation
The Transplant Company®

[redacted]

August 14, 1997

Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

Subject: **MAJOR AMENDMENT AADA # 64-195**
SangStat COSM, Cyclosporine Oral Solution for Microemulsion 100 mg/mL

Dear Sirs:

This amendment is being submitted in response to the Office of Generic Drugs' letter dated April 11, 1997. This letter transmitted comments regarding the chemistry review portion of the AADA # 64-195 for SangStat COSM, Cyclosporine Oral Solution for Microemulsion, 100 mg/mL (SangStat COSM).

SangStat has responded to each of the reviewer's comments. For ease of review, the reviewer's comments are reproduced in italics with the SangStat's response immediately following each respective comment. In addition, a copy of the Agency's April 11, 1997, correspondence is attached immediately after the Form FDA 356h (revision 4/97).

We respectfully request that this information is treated as confidential. We hope that the enclosed responses satisfactorily address your comments. Should you have additional questions, please contact me at (415) 688-2335.

Sincerely yours,

Hana B. Moran

Hana B. Moran, PhD
Senior Vice President
Regulatory Affairs and Quality Assurance

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Enclosures

1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

SangStat Medical Corporation
The Transplant Company™

November 21, 1996

507 info ol
Anne Marie H. Udell
12/26/96

ARCHIVAL COPY

Mr. Douglas L. 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

SUBJECT: **Original Abbreviated New Drug Application (AADA)**
Cyclosporine Oral Solution for Microemulsion, (COSM), 100 mg/mL

Dear Mr. Sporn:

Pursuant to Section 507 of the Food, Drug and Cosmetic Act and in the format of 21 CFR 314.50, SangStat Medical Corporation (SangStat) herewith submits an Abbreviated Antibiotic Drug Application (AADA) for Cyclosporine Oral Solution for Microemulsion, (COSM), 100 mg/mL. This Application is being submitted on behalf of SangStat Medical Corporation (SangStat) of Menlo Park, California. SangStat has contracted Eli Lilly and Company (Lilly) of Indianapolis, Indiana, to manufacture, package, and test the drug product in accordance with Current Good Manufacturing Practices (cGMP), Code of Federal Regulations (CFR), and compendial requirements. The Drug Substance is referenced in AADA # from , which will supply the new drug substance (NDS). SangStat has provided a letter from thorizing the FDA to refer to the above referenced AADA on our behalf.

Additionally, please refer to a January 17, 1996, meeting between Office of Generic Drugs (OGD) and SangStat during which the development and approval requirements of the above referenced subject of this submission were discussed.

In support of this Application, we are providing information outlined below (see index for and volume page):

- Index
- Application Form FDA 3439
- Basis for Submission
- Debarment, Conviction and Field Copy Certifications
- Comparison between the proposed drug and the reference listed drug (Neoral®, by Sandoz Pharmaceutical Corporation)
- Draft labels/labeling (four copies each in the archival [blue] and review [red] binders and one copy in the review [orange] binder)
- Demonstration of bioequivalence between the generic drug candidate and the listed reference drug (AUC and C_{max}, 90% confidence interval)
- Chemistry, manufacturing and controls information

1505 Adams Drive Menlo Park, CA 94025 Telephone: 415.328.0300 FAX: 415.328.8892

- Methods validation package (one copy in the archival [blue] binder, one copy in the review [red] binder.

The archival copy of this Application consists of 5 volumes.

Throughout this Application you will note that the formulation of the 100 mg/mL product is referred to as Item code . This is an identifier number and refers only to the formulation number assigned for this product (SangStat formulation numl and does not indicate a batch or a lot. The lot number D20571 designates final bulk product. The filled and packaged material has lot number D20571M. The supplies for the *in vivo* bioequivalence studies are labeled by a ıey possess a new Item code, P03508, and a new lot number CT06118. These latter numbers are listed in the clinical reports presented in section VI. of this Application

The bioequivalence studies comparing the SangStat COSM and the reference listed drug were conducted under fasted and fed conditions. The results have demonstrated a 90% confidence interval, for the logarithmic expression of bioequivalence data ($AUC_{0\text{-}36hr}$, $AUC_{0\text{-}\infty}$, and Cmax) for the range of 0.80 -1.25.

The formulation of the product in this Application differs from the formulation specified in FDA's published monograph on the reference drug with regards to inactive ingredients. As discussed in companion to this Application, the Application is approvable under the agency's regulations regardless whether it meets all requirements of the monograph. In addition, the drug substance differs from the monograph with regard to source organism. This has been addressed by n their AADA # ( ), and will only be summarized in the Bioequivalence and Raw Materials sections to facilitate the review. Although FDA need not amend the existing monograph to approve the ıADA or this Application, SangStat has proposed that the agency amend the monograph following approval of both d SangStat's Cyclosporine AADAs.

No patent certification or exclusivity information is provided with this Application because the Application is submitted under Section 507 of the Food, Drug and Cosmetic Act.

SangStat respectfully requests 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 released to an applicant without written consent by SangStat 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 Hana Berger Moran at (415) 328-0300 ext.135 or Dr. Philippe Pouletty at (415) 328-0300 ext.129.

Sincerely,

Hana Berger Moran

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

Philippe Pouletty, M.D.
Chairman and CEO

Comment 1.

The application does not include any data to demonstrate that the analytical methodology used for release and for stability will resolve the known impurities of Cyclosporine. Specifically:

Page(s) 5

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Additionally six (6) sample containers from exhibit batch Lot Number D20571 are being sent to:

Food and Drug Administration
Beltsville Research Facility
Attention: Valerie Flournoy (HFD-910)
8501 Muirkirk Road
Laurel, MD 20308

(Telephone: 301-827-8054)

A copy of the latest Certificate of Analysis accompanies the samples