memos

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 2, 1994
TO: Division File, NDA 50708 and NDA 50709
THROUGH: James Farrelly, Ph.D., Supervisory Pharmacologist 2/2/94
FROM: Lauren Black, Ph.D., Reviewing Pharmacologist 2/2/94

SUBJECT: Clarification of the Sponsor's Phase 4 committments

The sponsor Phase 4 committment letter, telefaxed on January 31 was unclear regarding one point of remaining pharmacology and toxicology committments, the committment to conduct a 13-week study dietary study in mice. The purpose of requiring this study is to address deficiencies in the study design of the 80-week carcinogenicity study in mice which was submitted to the NDA in incomplete form.

During a teleconference conducted on 2/2/94, this point was clarified by the sponsor. They have agreed to meet this requirement, and agree the language regarding this committment was unclear in their previous letter. They are in the process of preparing a second letter, clarifying this Phase 4 committment in writing. We expect this letter to be telefaxed today.

From the standpoint of pharmacology and toxicology, NDA 50708 and NDA 50709 are approvable.

Facsimile sent on 1-25-94 and again on 1-26-94. C. Broadnax

Memorandum of Telephone Facsimile Correspondence

Date: January 25, 1994

To: Jerry Johnson, Ph.D.
Fujisawa USA, Inc.
Fax: 708-317-7286

From: Carole Broadnax, R.Ph. - Consumer Safety Officer CB 1-25-94
Division of Antiviral Drug Products, FDA

Through: Donna Freeman, M.D. - Supervisory Medical Officer DSF 1/25/94
Division of Antiviral Drug Products, FDA

Re: NDA 50-708 and NDA 50-709/Prograf Capsules and Ampules

Subject: Phase IV Requests

We have the following requests regarding the phase IV development of Prograf. Although approval of your NDA is not contingent upon your response to these comments, we would appreciate a response as soon as possible.

Clinical

1. Please conduct pediatric studies to better characterize the pharmacokinetics, safety and efficacy in children.

2. You are encouraged to commit to the development of an oral liquid formulation which might be more suitable for use in small children than the proposed capsules.

3. Please create a registry for collecting safety data on pregnancies occurring during the use of tacrolimus.

4. Please collect data concerning overdosage with tacrolimus.

5. Please collect long-term safety and efficacy data from the ongoing portion of study GHBA-157 (up to 24 months post-transplant) and patients who received tacrolimus in Study FPC-FK506-7.

6. Please conduct a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.

Pharmacology/Toxicology

You must address the characterization of the potential risk of carcinogenicity in mice as part of your phase 4 commitments. A 2-year carcinogenicity study in rats is also expected to address this issue.

The following comments pertain to the incomplete nature of the data submitted in the report of the 80-week carcinogenicity study in mice. It is not clear from the submitted data that sufficient drug exposure from the dietary route was attained. Further analysis of the 80-week study and an additional dietary toxicity study will be required to evaluate this issue.

Please submit for our review as detailed below (a) the results of the reevaluation of the 80-week study, and (b) the results from the second 13-week study in mice, together with the results of the final report on the 2-year study in rats. The same types of analyses indicated here for the study in mice should be conducted and reported for the study in rats. Following our review and consideration by the Executive Subcommittee of the Carcinogenicity Assessment Committee, a final decision about the adequacy of the 80-week mouse study will be made. You should be aware that it is possible that a second carcinogenicity study in mice may still be required if the completed results of the current rodent studies do not provide adequate data for a secure assessment of the human carcinogenic risk.

1. Please submit reports of the histopathological analyses of all the mice in the 80-week carcinogenicity study you have conducted and submitted to the FK506 NDA's. You should re-evaluate this study based on the total data set. Additionally, please supply an analytical master table of all benign and malignant neoplasias seen on study. The table should list the following information for each mouse: sex; dose group; individual mouse number; tumor status (benign or malignant); organ of origin; type(s) of neoplasm(s); intercurrent or terminal death; and, in the case of intercurrent deaths, the week of death and the pathologist's attribution of the cause of death. This table should be used as a source table for your analyses and supplied as part of the study summary.

2. Please perform a 13-week dietary range-finding study in mice, using whole blood drug levels to monitor pharmacokinetics, including areas under the curve (AUC_{0-24}). Doses of 3 mg/kg and higher should be evaluated. In this study, the use of ultra-clean conditions should be considered, as immunosuppressive doses are the intention of human treatment. The goals of this study would be to identify the MTD, to characterize the profile of FK506 toxicity in male and female mice from the dietary route, and to compare mouse versus human exposure based on whole blood drug levels.

3. Please consider using a database management program (such as Paradox for Windows) to generate the requested tables and analyses. Once entered, the data can be sorted based on primary and secondary terms to yield summary

tables. Disks containing this database would be useful in increasing the efficiency of the FDA review.

Biopharmaceutics

1. Please conduct studies to determine the pharmacokinetics of tacrolimus in children. The differences in the IV and oral doses administered to pediatric and adult patients in your controlled studies and the respective differences attained in plasma trough concentrations indicate that the pharmacokinetics of tacrolimus are different in children and adults, and these differences need to be characterized.

2. Please continue your investigation of the relationship between tacrolimus whole blood/plasma concentrations and its efficacy/toxicity.

3. Please submit additional data to support a claim of dose proportionality for tacrolimus. Dose proportionality in renal transplant patients was not supported by the data submitted to the NDA, and the dose proportionality of tacrolimus in liver transplant patients was not documented.

4. Please conduct a protein binding study to definitively establish the protein binding of tacrolimus. The results of published studies (Nagasa and Jusko) of protein binding differ.

5. Please conduct studies to fully characterize the metabolic pathway of tacrolimus and its metabolites.

6. Because tacrolimus will be used in patients on multiple medications, the following issues regarding drug interactions should be addressed:

   a) Because evidence that tacrolimus is metabolized by the cytochrome P450IIIA family suggests the potential for drug interactions with other substrates for this enzyme, please conduct *in vitro* drug interaction studies (using human hepatocytes, human liver slices, or human microsome preparations) to screen for possible interactions with drugs to be used concomitantly with tacrolimus. Based on the *in vitro* results, *in vivo* drug interaction studies with "key" drugs should be conducted.

   b) Please conduct a drug interaction study in multiple subjects to confirm your impression that there may be a drug-interaction between clotrimazole and tacrolimus. The publication submitted to the NDA's (Mieles, et al.) contained data from only one subject.

c) Please submit additional *in vivo* data to refute the statement that tacrolimus should be dosed separately from antacids. This conclusion is made by the authors of the "In-vitro Interaction of a Novel Immunosuppressant, FK 506 and Antacids" study (J Pharm Pharmacol 1991; 43:574-577), but is inconsistent with your assertion that there is no evidence from this publication that supports a potential drug interaction between tacrolimus and antacids.

7. Please consider conducting a multiple dose study to demonstrate bioequivalence between 1 and 5 mg tacrolimus capsules when administered as a 5 mg dose, i.e. five 1 mg capsules and one 5 mg capsule. Comparisons of single and multiple dose pharmacokinetics using clinical bioequivalence data show that single dose studies are more sensitive for detecting change in rate and extent of absorption. However, multiple dose studies are more representative of clinical drug use.

8. Please further define the lack of a role of bile in the absorption of tacrolimus.

9. Please evaluate the absorption of tacrolimus with respect to: i) various diet compositions; and ii) timing of food ingestion.

10. Please submit for review on completion of the study the data being collected currently in your ongoing study to determine the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.

11. Please determine the intra-subject variability of tacrolimus.

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact Carole Broadnax at (301) 443-9553 if you have any questions regarding the contents of this transmission.

CC:
NDA 50-708 & NDA 50-709
Division File

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 10, 1993
TO: Division File, NDAs 50-708 and 50-709
FROM: Dr. Lauren Black, Reviewing Pharmacologist 12/13/93
J. Farrelly 12/14/93

SUBJECT: Phase 4 Committments for Fujisawa, sponsor of FK506

The sponsor submitted the results of the 80-week carcinogenicity study in mice to the NDA and proposed an interpretation for the label. The suggested language indicated that there was no risk of carcinogenicity associated with FK506. However, in our opinion, the current label for FK506 should read: "To date, no studies adequately evaluating the carcinogenicity of FK506 have been submitted. Studies are currently underway in mice and rats." Reasons for this interpretation follow (also, see review under separate cover).

The data contained in this study (2 control groups; and 3 dosed groups; groups 1-5, respectively) provide evidence that 1) FK506 was absorbed from the diet; 2) showed minimal toxicities in the group 5 (high dose) males and slight toxicities in group 5 females; 3) was associated with some toxicities such as lymphoid atrophy, reduced numbers of pancreatic islets, histopathologic changes in males reproductive organs, and reduced group mean body weight gains in the first 52 weeks of the 78-week study; and 4) was associated with higher incidences of pleomorphic lymphoma (likely in association with immunosuppression) in the high dose group. But the interpretation of the study results is made difficult by several factors.

- The sponsor asserted that decreased body weight gains in the mid and high dose males, as well as the high dose females, supported the fact that the MTD was reached. Although individual animal weights were provided, a table of individual weight gains (broken down by intervals and group) would be necessary to link this effect to other potential toxicities of fk; this was not provided. The fact that decreased body weight gains or weight losses were not seen in these groups late in the study (when toxic effects of fk should have been accumulative), weakens this assertion.
- The profile of fk toxicity in the mouse under sub-chronic or chronic conditions has not been adequately explored, making attribution of mortalities difficult, especially in cases of infections and early deaths. The doses were selected from dose-ranging studies which failed to demonstrate toxicity in females, and showed minimal toxicity in males. Overall, neither the toxicity data, mortality rates, nor the pharmacokinetic data, supported the sponsor's assertion that the MTD was acheived.
- Pharmacokinetic measures were performed in a 13-week range finding study, and measured levels in plasma (90-98% of the drug is found in formed blood elements). While these levels showed some drug was absorbed from the diet, no comparisons can be made with human whole blood exposures.
- The 80-week, rather than 104-week, overall duration of exposure was further reduced by a high-rate of mortality due to amyloidosis, especially towards the end of the study. It is not clear whether a sufficient approximation of life-time exposure was achieved in a sufficient number of mice to assure that carcinogenic potential was characterized.
- Lymphomas are known to arise under a number of immunosuppressing drug therapies or disease conditions, both in various animal species as well as humans. The higher incidence of lymphomas in the high dose groups is probably clinically significant.
- All tissues were not evaluated in the mid and low dose groups, obscuring the interpretation of an incidence of liver tumors in the low and mid dose groups.

CONCLUSIONS:
The mouse carcinogenicity study may be inadequate because the MTD may not have been reached and is incomplete because full histopathological analysis has not be conducted. The resolution of these limitations will require negotiations between the sponsor and FDA. Solutions will result in Phase 4 commitments, rather than holding up marketing approval for this drug, as previously agreed by the FDA and the sponsor.

The following suggestions may be implemented to solve this problem of adequately characterizing the carcinogenic risk. The sponsor is currently conducting a 2-year carcinogenicity study in rats. If this study is adequately designed and conducted (no information has been submitted as yet), and is interpretable, then it should be adequate from a regulatory standpoint to simply complete histopathological analyses on mid and low dose mouse tissues, and submit a full report of the mouse study. Additionally, a 13-week dose-ranging study with appropriate measures of pharmacokinetic parameters should be conducted to evaluate the MTD and determine how close the high dose used in the 78-week study was to the MTD, and the relevance of the dosing to clinical exposures.

REQUIREMENTS for PHASE 4:
1) Please supply reports of the histopathological analysis of all of the mice in the study and reevaluate the study based on the total data set. Additionally, please supply an analytical table of all benign and malignant neoplasias seen on study. The table should list the following information for each mouse: sex, dose group, individual mouse number, tumor status (benign or malignant), organ of origin, type(s) of neoplasm(s), intercurrent or terminal death, and in the case of intercurrent deaths, the week of death and the pathologist's attribution of the cause of death. This should be used as a source table for analyses made by the sponsor, and supplied as part of the study summary.

2) Please perform a 13-week dietary range-finding study in mice, using whole blood levels to monitor pharmacokinetics and obtain values of Areas Under the Curve (AUC_{0-24}). Doses higher than 3 mg/kg should be evaluated. In this study, the use of ultra-clean conditions should be considered, as immunosuppressive doses are the intention of human treatment. The goal of this study would be to identify the MTD, and to characterize the profile of fk toxicity in mice from the dietary route in males and females. The results of the reevaluation of the 80-week study and the results from the second 13-week study should be submitted together with the results of the final report of the 2-year study in rats for FDA consideration. Based on these results, discussions with the sponsor, and consideration by the Executive Subcommittee of the Carcinogenicity Assessment Committee, a final decision about the adequacy of the 80-week study will be rendered. The decision of the CAC executive committee may supercede these remarks: it is possible that a second mouse study may still be required if the completed results of the current rodent studies do not provide adequate data for a secure assessment of human carcinogenic risk.

RECOMMENDATIONS:
3) To generate the table and analyses requested, please consider using a spreadsheet program such as Paradox or Lotus 1-2-3 for IBM-compatible computers. Once entered, the data can be sorted based on primary and secondary terms to yield summary tables. Disks recording this database would be especially useful in increasing the efficiency of FDA review.

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: January 13, 1994

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Dr. Tony El-Hage - Division of Scientific Investigations (DSI)

Division of Antiviral Drug Products/FDA/HFD-530
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Clinical Site Inspections

Background: On January 12, 1994, I spoke with Carol Ann Currier of DSI about the status of the clinical site inspections for Prograf. Of the four sites (Dallas, New York, Los Angeles and Omaha) to be inspected, the New York site was the only site inspection that was completed and NAI. The other three sites were pending inspection.

Issues for Discussion:
At the request of Dr. Feigal, Director, DAVDP, I contacted Dr. El-Hage to let him know that we may be ready to approve the product by the end of the next week and whether that would be a problem. Dr. El-Hage stated that this would be "fine" with him. He added that he would keep the Division updated, after the NDAs were approved, as the clinical site inspections are completed.

The conversation was cordial throughout.

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
NDA Package

Broadnax

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: November 9, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS:

Fujisawa USA, Inc.
Jerry Johnson, Ph.D. - V.P. Regulatory Affairs
Jim Shook, Ph.D. - V.P. Research & Development

Division of Antiviral Drug Products/FDA/HFD-530
Donna Freeman, M.D. - Supervisory Medical Officer
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer
Carole Broadnax, R.Ph. - Consumer Safety Officer

FDA Advisory Committee Office
Lee Zwanziger

SUBJECT: Advisory Committee Meeting and Dr. Barry Kahan

Background: This teleconference was initiated to discuss Dr. Barry Kahan's participation as a consultant to the FDA at the November 22, 1993, Antiviral Drug Advisory Committee Meeting.

Issues for Discussion:
Ms. Zwanziger discussed the need for balanced opinions as a criterion for selecting consultants to the Advisory Committee. Physicians on both sides of the issue were invited. The purpose of the meeting is to let the agency hear the various scientific interpretations of the data presented. In addition, the financial interest of each consultant is weighed against the agency's need for that person's degree of expertise.

Dr. Freeman stressed that the Committee advises only the Division. Regulatory decisions are made by the agency. The consultants may or may not be allowed to vote.

Ms. Zwanziger explained the procedure for nominating Advisory Committee members and inviting consultants. Committee members are nominated. Consultants are not members of the standing committee. Names for consultants are

sought from experts in the field. They go through an initial conflict of interest (COI) screening (financial) and are checked for availability on the day of the proposed meeting.

FUSA stated that Dr. Kahan was a well known paid consultant of Sandoz Pharmaceuticals. He has been documented to have negative views of FK506. Dr. Thomas Starzl will be at the Advisory Committee meeting in the audience and the proceedings may be disrupted if there is a heated confrontation between Drs. Starzl and Kahan. The meeting may not be a fair hearing.

Ms. Zwanziger responded that all financial interests have been reported by Dr. Kahan and others and that the FDA is considering them. Regarding intellectual bias, the agency would like to have knowledgeable and neutral people. When this is not possible the agency seeds to balance opposing points of view. Regarding security, possible disruptions would not be a new experience. Dr. Starzl is welcome to speak at an open public hearing if he so chooses.

FUSA commented that financial interest and intellectual bias place Dr. Kahan far from the norm of an Advisory Committee. Ms. Zwanziger responded that the agency has looked at Dr. Kahan's financial background.

FUSA suggested Dr. Paul Keown of Vancouver as a possible consultant for the Advisory Committee.

Dr. Freeman stated that the list of invitees was a small portion of the people actually approached. The final list was the best panel the FDA could assemble given the time constraints. FUSA should be assured that the Division will talk to the Advisory Committee Chair to make her aware of possible divisive issues and tangents and to allow her to keep the meeting on track.

Dr. Cavaillé-Coll brought to FUSA's attention that Dr. Colambiani of Johns Hopkins was an investigator in the FK506 studies and would be one of the consultants at the Advisory Committee. FUSA responded that they were not sure that this information would cover their concern about Dr. Kahan. In Dr. Shook's opinion, Dr. Starzl would be needed to counterbalance Dr. Kahan.

FUSA stated that they would submit a letter stating their opposition to Dr. Kahan as a consultant to the Antiviral Advisory Committee. Ms. Zwanziger commented that if the letter was sent to her then it would be available under the FOI Act. The letter could be submitted to the Advisory Committee where it would be made available to all the members.

Dr. Freeman stated that it has not yet been determined which consultants might be able to vote. The Advisory Committee Chair may also request a vote of the consultants. FUSA requested that Dr. Kahan not be allowed to vote. Ms. Zwanziger stated that FUSA's request was duly noted.

The conversation was cordial throughout.

concurrence:
DFreeman/11-15-93
Marc Cavaille-Coll/11-10-93
CBroadnax/RD 11-9-93/Edit 11-17-93

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/DD/DFeigal
HFD-530/SMO/DFreeman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Biopharm/ADurantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax
HFD-9/LZwanziger

Broadline

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: November 8, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
Ramona Krailler, Ph.D. - Regulatory

Division of Antiviral Drug Products/FDA/HFD-530
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer

SUBJECT: Protocol Violators in Study -157

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Dr. Cavaillé-Coll called Dr. Krailler to request the following information:

Please provide the one year patient and graft survival [simple proportions] broken down by protocol violators (those who received azathioprine, ALG or ATG) versus non-violators.

1) Azathioprine Administration
24.7% (66/267) of the patients assigned to FK506 also received at least one dose of azathioprine [see Table 22, appendix S24]. The majority of these patients received azathioprine as a result of experiencing an adverse event while on FK506 therapy.

2) ALG Administration
9 patients received ALG for 5-11 days. All but 2 of the adminstrations coincided with interrruptions in FK506 therapy [See Table 24 and Appendices S22 and S23].

3) ATG Administration
14 of the FK506 patients (5.2%) received ATG for between one and 15 days, 2 due to interruptions in FK506 therapy, 2 due to the treatment of GVHD and acute rejection. 10 were due to routine post-transplant prophylactic immunosuppression.

The conversation was cordial throughout.

concurrence:
Marc Cavaille-Coll/11-10-93
CBroadnax/RD 11-10-93

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/ASMO/DFreeman
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/CSO/CBroadnax

Broadnax 1

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: October 14, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
Jerry Johnson, Ph.D. - V.P., Regulatory Affairs
Ramona Krailler, Ph.D. - Regulatory Affairs

Division of Antiviral Drug Products/FDA/HFD-530
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Rough Draft of the Advisory Committee Briefing Document/Status of Data for -45 Study

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Background: On October 13, 1993, Dr. Krailler sent by facsimile FUSA's draft of their advisory committee briefing document. FUSA made a request for our comments on this document. This teleconference was initiated in response to that request.

Issues for Discussion:

Advisory Committee Briefing Document

1. It would be helpful to provide the committee members with copies of the written protocols for study -7 and -157, as an appendix to the briefing document, with a cover memo indicating that this is for reference only. Some members may be interested in certain details of the study that may not be present in the summary package.

2. FUSA should include detailed information on dosing, schedule and monitoring used in the CBIR at each clinical site in study -7 and study -157. This information would be of interest to those members of the committee who would question whether an optimal cyclosporin based regimen was used in the active control arm of each study. FUSA might include a summary in the text and an appendix for the reports.

3. FUSA should include in Clinical Studies section a detailed description of the FK506 doses, schedules and monitoring used in studies -7 and -157. In particular, the changes made in the initial IV dosing during the conduct of the study should be described and the number of subjects treated under each of these different regimens should be included.

4. Under section IV. RECOMMENDED DOSING AND TROUGH LEVELS some attention should be given to special dosing recommendations in children and to special dosing recommendations according to status of post-op liver allograft function.

5. In section I. OVERVIEW the indication sought in this application should be made clear. FUSA agreed to clarify the indication.

6. We would prefer that the term not be used to describe FPC- which is now listed only as a supportive study. It might be better to remove all reference to this study from the information package. Frankly, we do not consider this study as supportive of the indication now sought in the NDA. Uncontrolled experience in a population different than that which is the target for the proposed indication, does not belong in this package. The FDA does not intend to ask the committee to address any questions concerning the use of

Dose Optimization Study (-45)

1. FUSA agreed to submit an updated protocol including all amendments for biopharmaceutic and biostatistician review.

2. FUSA agreed to submit a study report by Monday, October 25, 1993.

concurrence:
Marc Cavaille-Coll/ 10.18.93
CBroadnax/RD 10-18-93
cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Micro/HOhanian
HFD-530/Biopharm/ADurantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax

COPY

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: October 1, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
Ramona Krailler, Ph.D. - Regulatory
Jerry Johnson, Ph.D. - V.P.-Regulatory
Don Buell, M.D. - Clinical Leadership
Angela Haberak

Division of Antiviral Drug Products/FDA/HFD-530
Marc Cavaille-Coll, Ph.D., M.D. - Medical Reviewer
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Proposed 90-day Safety Update

Background: On September 10, 1993, FUSA sent by facsimile a description of their proposed 90-day safety update for NDA 50-708. FUSA requested a teleconference to discuss this proposal. This teleconference was initiated by the FDA at FUSA's request.

Topics for Discussion:

1. The first priority is fine. FUSA should not add data from the has been withdrawn. If data is incorporated into the submission, it would not be reviewed.

2. The second priority is fine. FUSA should not include data from the study or follow-up data.

3. The third priority is fine.

4. Fourth priority: The Pittsburgh data is interesting but the data are not validated. This priority should follow behind the sixth priority.

5. The fifth priority should be the fourth priority.

6. Sixth priority: FUSA should have the degree of severity of neurotoxicity and nephrotoxicity measured on a WHO scale.

7. FUSA will submit the 90-day safety update by October 29, 1993.

8. FUSA will call next week regarding the status of the clinical sites readiness for inspection.

8. FUSA will provide preliminary data on the dose optimization study (-45) after October 8, 1993. They proposed submitting the final clinical report by December 1, 1993.

The conversation was cordial throughout.

concurrence:
MCavaille-Coll/init/10-4-93
CBroadnax/RD 10-1-93/Edit 10-4-93

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/DFreeman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Micro/HOhanian
HFD-426/Biopharm/ADorantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax

MEMORANDUM OF TELEPHONE CONVERSATION

IND:

DATE: September 28, 1993

COPY

PRODUCT: FK506

INDICATION: Solid Organ Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
Ramona Krailler, Ph.D. - Regulatory Affairs
Ihor Bekersky, Ph.D. - Dir. Pharmacology & Toxicology

Division of Antiviral Drug Products/FDA/HFD-530
Lauren Black, Ph.D. - Reviewing Pharmacologist
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Reproductive Toxicity Studies - Pharmacologist's Review dated August 17, 1993.

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Background: On September 16, 1993, FUSA was sent by facsimile the toxicologist's interpretation of the reproductive studies (attachment). A request to have a teleconference with FUSA was make in order to discuss these issues in reference to the upcoming label for NDAs 50-708 and 50-709 for Prograf capsules and ampules. This teleconference was initiated in response to that request.

Issues for Discussion:

1. FUSA agreed that the interpretation was pretty accurate.

2. Please provide a brief synopsis of reproductive toxicity studies for use in the label. Submission of the proposed wording is suggested after the advisory committee meeting. Highlight dose relationships between clinical and animal doses. Also, highlight the dose relationships between reprotoxicity seen at one-half the clinical exposure equivalent and maternal toxicity seen at 3-fold higher doses.

3. FUSA will be submitting mouse carcinogenicity reports as well as other reports to the IND as Pharmacology Amendments with a letter to NDA 50-708 as cross-reference.

The conversation was cordial throughout.

concurrence:
LBlack/init/10-19-93
CBroadnax/RD 10-19-93

cc:
NDA Orig. 50-708 and 50-709/IND Orig. 34,654
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/Pharm/LBlack
HFD-530/CSO/CBroadnax

COPY

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: September 23 and 24, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
James Shook, Ph.D. - V.P. Research & Development
Donald Buell, M.D. - Director, Infectious Diseases
William Fitzsimmons, Pharm.D. - Clinical R&D
Ramona Krailler, Ph.D. - Regulatory

Division of Antiviral Drug Products/FDA/HFD-530
Donna Freeman, M.D. - Supervisory Medical Officer
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Request to Withdraw Proposed Indication

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Background:

At the 45 day filing meeting held on August 31, 1993, it was determined that the rejection prophylaxis following primary liver transplantation indication was reviewable, but that the NDA did not contain a controlled safety database for the proposed indication for the treatment
indication). An internal meeting was held on September 23, 1993 to discuss this issue further. At the conclusion of this meeting, it was decided that FUSA should be presented with the following options:

1. Send FUSA a letter explaining that the indication was not fileable but that the primary liver indication was fileable.

2. Submit an efficacy supplement for the indication including additional information to what has been provided after approval of the primary liver indication has been granted.

3. Withdraw the indication from the NDA.

The September 23 and 24, 1993 teleconferences with FUSA were initiated to discuss these options.

Issues for Discussion:

September 23, 1993 Teleconference

1. Dr. Freeman stated that there was concern that the indication would not make it at an Advisory Committee Meeting due to several factors including flawed datasets.

2. Elements that an Advisory Committee would consider serious flaws in the study are as follows:

   a. At least 40 of the 125 patients reported were not initially enrolled in the study but were allowed to receive FK506 on a case-by-case compassionate basis before the written protocol was finalized.

   b. Unplanned interim look from April 1991 to October 1991. Protocol is still ongoing and more than 400 patients have been enrolled.

   c. The historical controls were assembled after the patient data was analyzed. The re-transplant surgical controls do not describe the natural history of the patients in study

   d. There is not control safety and toxicity data for comparison. There is also insufficient demographic and baseline clinical data to verify whether the control groups are at all comparable to the treatment group.

   e. Entry criteria protocol violators: Some patients did not receive a trial of OKT3 or Imuran before enrollment in the study and therefore did not meet the criteria for

3. FUSA was asked to consider withdrawing the indication and to devote attention to the primary indication. If withdrawn, the indication could be resubmitted with additional information than in its present form as an efficacy supplement once the NDA was approved for the primary liver indication. This would be the most efficient solution.

4. Dr. Freeman stated that the FDA would like to work with FUSA to get the NDA review process done efficiently and to give FUSA the agency's concerns promptly. She emphasized that the 60-day filing clock ended on September 24, 1993 and that we would need to come to an understanding before close of business on September 24th.

5. Dr. Krailler stated that she was not prepared to give a response at this time. She suggested, and we agreed, to have a follow-up teleconference on September 24, 1995 at 11:30 am.

September 24, 1993 Teleconference

1. FUSA argued that they receive calls on a daily basis requesting the use of FK506 for the indication. Their plans are to include the study patients in a safety update, therefore, the label revisions are reflective of actual drug use in the clinical and the commercial setting. Also, FUSA has looked at other available agents and they would like to be competitive with cyclosporine.

2. Dr. Freeman emphasized that the label should reflect the "approved" indications. The agency can only review what is in the NDA and not what is planned to be submitted at a later date (ie, a safety update). Dr. Cavaillé-Coll stated that the NDA did not contain sufficient information to permit a substantive review of the indication. This indication should be the subject of an efficacy supplement which would include additional information to what has been provided. Dr. Freeman offered to work with FUSA on appropriate labeling based on the information in the NDA.

3. FUSA agreed to withdraw the indication from the NDA. They will submit a letter of understanding.

The conversation was cordial throughout.

concurrence:
DFreeman/12-15-93
Marc Cavaille-Coll/12-15-93
CBroadnax/RD 12-15-93

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/SMO/DFreeman
HFD-530/MO/MCavaille-Coll
HFD-530/CSO/CBroadnax

Broadnax

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 50-708/50-709

DATE: September 13, 1993

PRODUCT: Prograf (tacrolimus) Capsules/Ampules

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc.

PARTICIPANTS: Fujisawa USA, Inc.
Jerry Johnson, Ph.D. - V.P. Regulatory Affairs
Don Buell, M.D. - Clinical Program

Division of Antiviral Drug Products/FDA/HFD-530
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Lymphoproliferative Disorder (LPD)

Background: On September 10, 1993, Dr. Jerry Johnson sent by facsimile a request to have a teleconference to provide us with information relating to lymphoproliferative disorder (LPD) in patients receiving FK506. This teleconference was initiated in response to that request.

Issues for Discussion:

reported that at the 4 cases of LPD have been reported in pediatric patients less than 1 and 2 years of age. One patient was in the -045 study (primary therapy) and 3 were under therapy. One out of the three children on therapy died after one week on FK506. Other children were on FK506 for 4 and 9 months. The LPD after post-mortem examination was not considered an FK506 case.

At , 53 patients in this age range received cyclosporine from October 1988 to August 1993. Nine deaths occurred out of 53 patients with cyclosporine compared with 4 deaths out of 29 for FK506.

LPD has not been seen in the primary therapy study (-7) in 16 patients less than 2 years.

LPD has occurred at a higher incidence during therapy. Four cases appeared out of 36 patients less tha years old. Data has been collected through March 31,

1993. FUSA does not yet have a complete database. FUSA will submit more information with the 90 day NDA safety update.

University of Pittsburgh Data
The University of Pittsburgh transplantation database contains 103 patients less tha 2 years old and 90 patients less than 1 years old. Only 10 patients are included. Eight cases of LPD occurred out of 103 patients for a crude rate of 7.8%. In contrast, among 2-18 year olds, LPD occurred in out of 199 patients or 4.5%.

FUSA Data compared with Pittsburgh Data
FUSA - for patients less than 2 years old, 12 cases of LPD occurred out of 163 patients or 7.4%.

A Pittsburgh paper published in the Journal of Transplantation, Vol. 45, p. 719, 1988 (Monto Ho) states that the general incidence of LPD was 4%-5% in children 0-18 years of age under cyclosporine. 2 cases occurred in children less than 2 years of age with cyclosporine. In the 1-2 age group, there was a low incidence of seropositivity for EBV. Under potent immunosuppression, however, LPD will come out.

In conclusion, stated the FUSA would follow-up with written minutes of this teleconference to the NDA file. Dr. Cavaillé-Coll requested the FUSA factor time to follow-up and to please keep us informed. FUSA agreed to continue to gather information and to summarize the information in a facsimile. They will also follow-up with an IND safety report to IND and to this NDA 50-708.

The conversation was cordial throughout.

concurrence:
Marc Cavaille-Coll/init/10-19-93
CBroadnax/RD 10-19-93

cc:
NDA ORIG. 50-708/50-709 and IND Orig.
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Micro/HOhanian
HFD-530/Biopharm/ADorantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax

MEMORANDUM OF TELEPHONE CONVERSATION

NDA:	50-708/50-709
DATE:	August 12, 1993
PRODUCT:	Prograf (tacrolimus) Capsules/Ampules
INDICATION:	Prophylaxis and Treatment of Liver Rejection after Transplantation
SPONSOR:	Fujisawa USA, Inc.
PARTICIPANTS:	Fujisawa USA, Inc. Ramona Krailler, Ph.D. - Regulatory Division of Antiviral Drug Products/FDA/HFD-530 CB 8/12/93 Carole Broadnax, R.Ph. - Consumer Safety Officer
SUBJECT:	Request for Information/Assignment of Antibiotic NDA Numbers

I contacted Dr. Krailler to request the following information:

1. Timeline for the submission of the results of the dose optimization study in liver transplantation.

2. Written proposal for monitoring FK506 drug levels in patients should no approved/marketed assay be available when FK506 would be approved.

I emphasized that this information should be received by the 45-day filing meeting on August 31, 1993. Dr. Krailler agreed to submit the requested information by August 31, 1993.

As a result of discussions during the August 11, 1993 Orientation Meeting, I informed Dr. Krailler of the assignment of new antibiotic NDA numbers to the Prograf NDAs:

Capsules, 1 mg and 5 mg	OLD# 20-362/NEW# 50-708
Ampules	OLD# 20-283/NEW# 50-709

The conversation was cordial throughout.

cc:
NDA ORIG. 50-708/50-709
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Micro/HOhanian
HFD-530/Biopharm/ADurantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax

MEMORANDUM OF TELEPHONE CONVERSATION

COPY

NDA: 20-362 50-758

DATE: August 4, 1993

PRODUCT: Prograf (tacrolimus) Capsules - FK 506

INDICATION: Prophylaxis and Treatment of Liver Rejection after Transplantation

SPONSOR: Fujisawa USA, Inc. (FUSA)

PARTICIPANTS: Fujisawa USA, Inc.
Ramona Krailler, Ph.D. - Regulatory

Division of Antiviral Drug Products/FDA/HFD-530
Marc Cavaillé-Coll, M.D., Ph.D. - Reviewing Medical Officer
Carole Broadnax, R.Ph. - Consumer Safety Officer

SUBJECT: Preparation for NDA Orientation Meeting/Conversion of Solid Organ Transplant Patients from Pittsburgh Made FK 506 capsules to Fujisawa Made FK 506 capsules (IND

Issues for Discussion:

NDA Orientation Meeting
At the request of Dr. Krailler, Dr. Cavaillé-Coll provided the following proposed agenda:

1. Introduction of the DAVDP review team to FUSA project management team.

2. Summary of claims and indications.

3. Summary of the clinical and statistical section.

2. Principal arguments and location of the supporting documentation in the application.

3. New information since the October '92 meeting. 12 month survival data and information on the historical control group for the study.

4. Summary of the animal toxicity (including animal PK if available) studies emphasizing target organs of dose limiting toxicities and levels and duration of animal exposure.

5. Toxicities associated with FK 506. What might predispose a patient to a toxicity (likelihood of experiencing a toxicity, etc.)

6. Summary of the PK of FK 506 and information on the blood level monitoring. Identify assays to be used and the status of the assays.

7. Brief discussion of the PK, safety and efficacy in subgroups including children and women.

(Note: The order of these items may be rearranged by FUSA to reflect drug development chronology.)

Regarding lines of communication, the CSO will be the point of contact for the FDA review team and the FUSA project management team. However, for questions of clarification, the reviewing statistician has traditionally called directly the FUSA statistician. Similar contacts may occur between the other disciplines. More substantial requests for information should be communicated through the CSO. On a routine basis, once a month or every 6 weeks, FUSA will compile their list of memorandums of teleconferences, facsimiles, etc. and submit them to the NDA as a chronologic diary. Further discussions about lines of communication will take place at the orientation meeting.

Conversion of Solid Organ Transplant Patients from Pittsburgh Made FK 506 Capsules to Fujisawa Made FK 506 Capsules (IND)

Dr. Cavaillé-Coll stated that had spoken with John McMichael of the University of Pittsburgh and had allowed Pittsburgh to switch all patients to the Fujisawa made 1 mg and 5 mg capsules. It was our expectation that FUSA would attend to the safety reports and to the use of FK 506 at Pittsburgh. FUSA should know which protocols exist at Pittsburgh. Dr. Krailler commented that the FK 506 capsules would be supplied by Fujisawa, Ireland. Dr. Cavaillé-Coll stated that FUSA and Dr. Starzl at Pittsburgh would receive a letter from us reiterating these points.

The conversation was cordial throughout.

concurrence:
MCavaille-Coll/Edit 8-6-93
CBroadnax/RD 8-6-93/Edit 8-9-93

cc:
NDA ORIG. 20-362
HFD-530/Division File
HFD-530/SMO/RBehrman
HFD-530/MO/MCavaille-Coll
HFD-530/Chem/MSeggel
HFD-530/Pharm/LBlack
HFD-530/Micro/HOhanian
HFD-530/Biopharm/ADurantes
HFD-715/Stat/LKammerman
HFD-530/CSO/CBroadnax

45-Day Filing Meeting
August 31, 1993

NDA:	50-708 and 50-709
DRUG:	Prograf Capsules and Ampules
SPONSOR:	Fujisawa USA, Inc. (FUSA)
ATTENDEES:	Rachel Behrman, M.D. Donna Freeman, M.D. Marc Cavaillé-Coll, M.D., Ph.D. Mark Seggel, Ph.D. Lauren Black, Ph.D. Angelica Dorantes, Ph.D. Carole Broadnax, CSO

Purpose

This meeting was held to determine if the NDAs were "sufficiently complete to permit a substantive review." (21 CFR 314.101)

Review Team Comments

The review team concluded that the NDAs were fileable.

Chemistry

1. No problems with filing the NDAs at this time.

2. Manufacturing inspections have been requested. FUSA has been in contact with Peter Smith of CDER Field Investigations.

3. FUSA will have to submit an extra copy of the abbreviated environmental assessment (EA) for review and a separate EA for the ampule formulation.

4. FUSA will have to submit dissolution profile information. Some manufacturing deficiencies were noted.

5. The labeling and nomenclature committee believes that the name Prograf is similar to the name Prozac, an antidepressant drug. Chemistry will be in contact with this committee.

Pharmacology/Toxicology

1. No problems with filing the NDAs at this time.

2. Further discussions with FUSA regarding reproductive toxicity will be needed.

Biopharmaceutics

1. The submitted studies are appropriate for filing.

2. Regarding the bioequivalene study, the results showed that 1x5 mg capsule vs. 5x1 mg capsule are not bioequivalent. Single administration of 5x1 mg capsule gives higher bioavailability than the 1x5 mg capsule.

3. FUSA needs to include in the package insert the results of the bioequivalence study.

4. FUSA should describe how FK506 level monitoring was conducted in the Japanese clinical trials (including analytical methodology). If available, FUSA should submit such information.

5. FUSA should submit a gender analysis of the pharmacokinetic data.

6. If possible, FUSA should submit a copy of the Japanese package insert translated to English.

Statistical

1. The NDA is missing an adequate evaluation of the safety parameters.

2. FUSA should provide a Kaplan-Meier estimate of safety parameters.

Clinical

1. The primary liver indication is reviewable. The NDA does not contain a controlled safety database for the indication.

2. Safety concerns include nephrotoxicity (which may not be totally reversible), neurotoxicity and a GI syndrome.

3. The current ELISA blood level assay is not appropriate for wide dessemination. The proposed may be made available if labeled for "Investigational Use Only" when the NDAs are approved. This might allow FK506 to be marketed before approval of the PMA for the assay.

4. The dose optimization study was completed in April 1993 but has not been analyzed. Some data will be submitted in late October.

At the conclusion of this meeting Drs. Cavaille-Coll and Dorantes and Ms. Carole Broadnax contacted Dr. Ramona Krailler of FUSA. The following issues were discussed and items requested:

1. The NDAs are fileable.

2. An advisory committee meeting is scheduled for the end of November. The following advisory committee members may sit on the immunosuppressive drug subcommittee: Drs. Meier, Modlin, Blaschke and Abernathy. FUSA agreed to submit a copy of the advisory committee information package to the FDA no later than 2 weeks prior to the subcommittee meeting.

3. FUSA should expect to receive facsimiles from this Division on a weekly basis which will contain requests for further information. FUSA should provide a timeline for a response to these requests (a response may be needed before the end of a 2 week period.)

4. FUSA should provide electronic data in Word Perfect for Windows/DOS format on diskettes. FUSA should provide data for the gender analysis of the pharmacokinetic data on diskette.

5. Dr. Qais Mekki (FUSA) will serve as Dr. Dorantes point of contact for biopharmaceutic review questions.

6. FUSA will submit a facsimile addressing the contents of a 90-day safety update package. Because the advisory committee may meet before 120 days, we wish to receive a 90-day update.

concurrence:
RBehrman/no comment
MCavaille-Coll/init/9-3-93
MSeggel/init/10-4-93
LBlack/no comment
ADorantes/init/9-9-93
CBroadnax/RD 9-3-93/Edit 10-4-93

cc:
NDA ORIG. 50-708 and 50-709
HFD-530
HFD-530 DD/DFeigal
HFD-530 SMO/RBehrman
HFD-530/SMO/DFreeman
HFD-530/MO/MCavaille-Coll

HFD-530 Micro/HOhanian
HFD-530 Chem/MSeggel
HFD-530 Pharm/LBlack
HFD-530/Stat/LKammerman
HFD-530/SBiopharm/JLazor
HFD-530/Biopharm/ADorantes
HFD-530/AADPM/RLillie
HFD-530/SCSO/ADeCicco
HFD-530 CSO/CBroadnax

NOV 3 1993

NDA 50-708
NDA 50-709

Fujisawa USA, Inc.
Attn: Hatsuo Aoki, PhD.
Chairman and Chief Executive Officer
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Aoki:

Reference is made to your new drug application (NDA) dated July 23, 1993 and August 3, 1993, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Prograf (tacrolimus) capsules and ampules, respectively.

Please refer to the September 24, 1993 teleconference between representatives of your firm and representatives of this Division.

We acknowledge the receipt of your correspondence dated September 24, 1993 agreeing to withdraw the proposed indication for

In compliance with this agreement, this proposed indication has been withdrawn.

As agreed to in the September 24, 1993 teleconference, the FDA will work with FUSA on the proposed labelling modifications and on obtaining further information about the indication.

Should you have any further questions concerning this IND, please contact Ms. Carole Broadnax at 301-443-9553.

Sincerely yours,

11-2-93

David W. Feigal, Jr., M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and
Research

Concurrences:
HFD-530/ADD/LRosenstein/ 10/26/93
HFD-530/SCSO/ADeCicco/init/10-21-93
HFD-530/SMO/RBehrman/init/10-19-93
HFD-530/ASMO/DFreeman/init/10-13-93
HFD-530/MO/MCavaillé-Coll/init/10-13-93
HFD-530/CSO/CBroadnax/RD 10-1-93/edit 10-22-93

cc:
NDA Original 50-708
NDA Original 50-709
HFD-530/Division File
HFD-530/DD/DFeigal
HFD-530/DepDir/LRosenstein
HFD-530/SMO/RBehrman
HFD-530/ASMO/DFreeman
HFD-530/MO/MCavaille-Coll
HFD-530/Pharm/LBlack
HFD-530/Chem/MSeggel
HFD-530/CSO/CBroadnax
HFC-130/JAllen
HFD-80 (GC)

General Correspondence

Co. Corres.

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (708) 317-8898 • Telefax (708) 317-7281

Fujisawa

Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

April 8, 1994

David W. Feigal, Jr., M.D., M.P.H., Director
Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Nicholson Research Center, 2nd Floor
5516 Nicholson Lane
Kensington, MD 20895

Re: NDA 50-708 PROGRAF™ (tacrolimus capsules)
THIS SUBMISSION: Phase 4 Commitments

Dear Dr. Feigal:

Please refer to the two letters submitted to this NDA by Fujisawa USA, Inc (FUSA) dated January 31, 1994 and February 2, 1994. These letters stated FUSA's agreement to the phase 4 requests of your Division.

This morning during a phone conversation with Ms. Broadnax, Dr. Black and Dr. Farelly of your Division, we were asked to clarify our agreements relating to the requests related to the mouse carcinogenicity and rat carcinogenicity studies.

Via this letter, I want to confirm that FUSA agrees to meet the FDA's requirements for carcinogenicity studies in both the mouse and the rat. We agree to work closely with Dr. Black and Dr. Farelly and others ... the FDA to ensure that these requirements are met. We acknowledge that additional carcinogenicity studies may be required.

If you have any other questions, please feel free to contact me at 708/317-8898 or Dr. Ramona E. Krailler at 708/317-1396.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs

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Fujisawa

Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

February 2, 1994

David W. Feigal, Jr., M.D., M.P.H., Director
Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Nicholson Research Center, 2nd Floor
5516 Nicholson Lane
Kensington, MD 20895

Re: NDA 50-708 PROGRAF™ (tacrolimus capsules)
THIS SUBMISSION: Phase 4 Commitments

Dear Dr. Feigal:

Please refer to a January 26, 1994 facsimile from Ms. Carole Broadnax, CSO, of your Division and to the submission to this NDA by Fujisawa USA, Inc (FUSA) dated January 31, 1994. The facsimile included a number of phase 4 commitments requested by your Division and the letter stated FUSA's agreement to these requests.

Today during a phone conversation with Ms. Broadnax, Dr. Black and Dr. Farelly of your Division, we were asked to clarify our agreement relating to the request to perform a 13-week dietary range-finding study in mice.

Via this letter, I want to confirm that FUSA agrees to perform such a 13-week study in mice and will work closely with Dr. Black and Dr. Farelly to ensure that the protocol meets the objectives of the study.

If you have any other questions, please feel free to contact me at 708/317-8898 or Dr. Ramona E. Krailler at 708/317-1396.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs

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Fujisawa

Jerry D. Johnson, Ph.D.
Vice President
Regulatory Affairs

January 31, 1994

David W. Feigal, Jr., M.D., M.P.H., Director
Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Nicholson Research Center, 2nd Floor
5516 Nicholson Lane
Kensington, MD 20895

Re: NDA 50-708 PROGRAF® (tacrolimus capsules)
THIS SUBMISSION: Phase IV Commitments

Dear Dr. Feigal:

Please refer to a January 26, 1994 facsimile from Ms. Carole Broadnax, CSO of your Division. This facsimile delineates a number of commitments which members of your Division have requested be made by Fujisawa USA, Inc., (FUSA) pursuant to final action on NDA 50-708.

This amendment provides responses to these requests. We have reproduced the request in bold typeface and respond to each request individually.

Clinical

1. **Please conduct pediatric studies to better characterize the pharmacokinetics, safety and efficacy in children.**

FUSA agrees that additional information regrading the use of FK506 in children is desirable and commits to develop such data.

2. **You are encouraged to commit to the development of an oral liquid formulation which might be more suitable for use in small children than the proposed capsules.**

FUSA agrees that development of an oral dosage form for use in small children is important and commits to develop such a dosage form provided it has appropriate quality, purity and manufacturing attributes. We have initiated evaluation of a number of dosage forms which have been found not to be appropriate for further development. FUSA commits to continue to identify and develop an oral dosage form appropriate for this special population.

3. **Please create a registry for collecting safety data on pregnancies occurring during the use of tacrolimus.**

As part of our post-approval surveillance program, FUSA agrees to collect safety data on pregnancies occurring during the use of tacrolimus. This will include spontaneous reports and literature review with additional follow-up, if necessary.

4. **Please collect data concerning overdosage with tacrolimus.**

As part of our post-approval surveillance program, FUSA agrees to collect data concerning overdosage with tacrolimus. This will include spontaneous reports and literature review with additional follow-up, if necessary.

5. **Please collect long-term safety and efficacy data from the ongoing portion of study GHBA-157 (up to 24 months post-transplant) and patients who received tacrolimus in Study FPC-FK506-7.**

FUSA agrees to collect at least 24 months post-transplant data on safety (serious adverse events) and efficacy (patient and graft survival) for patients receiving tacrolimus in both study GHBA-157 and study FPC-FK506-7.

6. **Please conduct a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.**

FUSA agrees to conduct a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction. Such a study has already been initiated and the protocol submitted to IND FUSA commits to discuss this protocol further with FDA at the earliest opportunity.

Pharmacology/Toxicology

You must address the characterization of the potential risk of carcinogenicity in mice as part of your phase 4 commitments. A 2-year carcinogenicity study in rats is also expected to address this issue.

The following comments pertain to the incomplete nature of the data submitted in the report of the 80-week carcinogenicity study in mice. It is not clear from the submitted data that sufficient drug exposure from the dietary route was attained. Further analysis of the 80-week study and an additional dietary toxicity study will be required to evaluate this issue.

Please submit for our review as detailed below (a) the results of the reevaluation of the 80-week study, and (b) the results from the second 13-week study in mice, together with the results of the final report on the 2-year study in rats. The same types of analyses indicated here for the study in mice should be conducted and reported for the study in rats. Following our review and consideration by the Executive Subcommittee of the Carcinogenicity Assessment Committee, a final decision about the adequacy of the 80-week mouse study will be made. You should be aware that it is possible that a second carcinogenicity study in mice may still be required if the completed results of the current rodent studies do not provide adequate data for a secure assessment of the human carcinogenic risk.

1. Please submit reports of the histopathological analyses of all the mice in the 80-week carcinogenicity study you have conducted and submitted to the FK506 NDA's. You should re-evaluate this study based on the total data set. Additionally, please supply an analytical master table of all benign and malignant neoplasias seen on study. The table should list the following information for each mouse: sex; dose group; individual mouse number; tumor status (benign or malignant); organ of origin; type(s) of neoplasm(s); intercurrent or terminal death; and, in the case of intercurrent deaths, the week of death and the pathologist's attribution of the cause of death. This table should be used as a source table for your analyses and supplied as part of the study summary.

FUSA agrees to submit the results of a reevaluation of the 80-week carcinogenicity study for FDA review. FUSA will reevaluate this study based on the total data set which will include complete histopathological analyses of all the mice (all tissues, all animals, all dose levels). FUSA will supply an analytical master table of benign and malignant neoplasms seen on study in the format requested by FDA.

2. Please perform a 13-week dietary range-finding study in mice, using whole blood drug levels to monitor pharmacokinetics, including areas under the curve ($AUC_{0\text{-}24}$). Doses of 3 mg/kg and higher should be evaluated. In this study, the use of ultra-clean conditions should be considered, as immunosuppressive doses are the intention of human treatment. The goals of this study would be to identify the MTD, to characterize the profile of FK506 toxicity in male and female mice from the dietary route, and to compare mouse versus human exposure based on whole blood drug levels.

FUSA will develop a protocol for a study to meet as many as possible of the objectives delineated in the above paragraph, i.e., to identify the MTD, to characterize the profile of FK506 toxicity in male and female mice from the dietary route, and to compare mouse versus human exposure based on whole blood drug levels. We will meet with FDA to discuss the protocol prior to initiation of the study. However FUSA believes that an MTD was attained in the 80-week mouse carcinogenicity study as shown by an increase in mortality, decreases in the body weight and body weight gains and non-neoplastic pathological changes. We are also prepared to discuss this further with you.

3. **Please consider using a database management program (such as Paradox for Windows), to generate the requested tables and analyses. Once entered, the data can be sorted based on primary and secondary terms to yield summary tables. Disks containing this database would be useful in increasing the efficiency of the FDA review.**

FUSA commits to consider using a database management program to generate the requested tables and analyses.

Biopharmaceutics

1. **Please conduct studies to determine the pharmacokinetics of tacrolimus in children. The differences in the IV and oral doses administered to pediatric and adult patients in your controlled studies and the respective differences attained in plasma trough concentrations indicate that the pharmacokinetics of tacrolimus are different in children and adults, and these differences need to be characterized.**

FUSA agrees that additional information about the pharmacokinetics of FK506 in children is desirable and commits to develop such data.

2. **Please continue your investigation of the relationship between tacrolimus whole blood/plasma concentrations and its efficacy/toxicity.**

FUSA commits to continue evaluating data from our clinical studies to investigate the relationship between tacrolimus whole blood/plasma concentrations and its efficacy/toxicity.

3. **Please submit additional data to support a claim of dose proportionality for tacrolimus. Dose proportionality in renal transplant patients was not supported by the data submitted to the NDA, and the dose proportionality of tacrolimus in liver transplant patients was not documented.**

FUSA commits to submit additional data to support dose proportionality.

4. **Please conduct a protein binding study to definitively establish the protein binding of tacrolimus. The results of published studies (Nagasa and Jusko) of protein binding differ.**

Studies to establish the protein binding of tacrolimus are ongoing. FUSA commits to submit these data when they are available.

5. **Please conduct studies to fully characterize the metabolic pathway of tacrolimus and its metabolites.**

FUSA commits to conduct studies to more fully characterize the metabolic pathway of tacrolimus and its metabolites. We believe FDA recognizes that complete characterization is a long-term project that may be limited by the current state-of-the-art in analytical methodology.

6. **Because tacrolimus will be used in patients on multiple medications, the following issues regarding drug interactions should be addressed.**

   a) **Because evidence that tacrolimus is metabolized by the cytochrome P450IIIA family suggests the potential for drug interactions with other substrates for this enzyme, please conduct *in vitro* drug interaction studies (using human hepatocytes, human liver slices, or human microsome preparations) to screen for possible interactions with drugs to be used concomitantly with tacrolimus. Based on the *in vitro* results, *in vivo* drug interaction studies with "key" drugs should be conducted.**

   b) **Please conduct a drug interaction study in multiple subjects to confirm your impression that there may be a drug-interaction between clotrimazole and tacrolimus. The publication submitted to the NDA's (Mieles, et al.) contained data from only one subject.**

Fujisawa

c) **Please submit additional *in vivo* data to refute the statement that tacrolimus should be dosed separately from antacids. This conclusion is made by the authors of the "In-vitro Interaction of a Novel Immunosuppressant, FK 506 and Antacids" study (J Pharm Pharmacol 1991; 43:574-577), but is inconsistent with your assertion that there is no evidence from this publication that supports a potential drug interaction between tacrolimus and antacids.**

FUSA commits to provide additional data on drug interactions with tacrolimus. This includes the use of both in vitro and in vivo tests. FUSA will work with FDA to define appropriate test systems. With respect to antacids, FUSA believes alternate interpretations of the data presented in the referenced publication are possible. FUSA commits to discuss this publication with FDA and, if continued discussion does not resolve this question, to submit additional in vivo data to better define the interaction, if any, between tacrolimus and antacids.

7. **Please consider conducting a multiple dose study to demonstrate bioequivalence between 1 and 5 mg tacrolimus capsules when administered as a 5 mg dose, i.e. five 1 mg capsules and one 5 mg capsule. Comparisons of single and multiple dose pharmacokinetics using clinical bioequivalence data show that single dose studies are more sensitive for detecting change in rate and extent of absorption. However, multiple dose studies are more representative of clinical drug use.**

FUSA commits to develop a multiple dose protocol to demonstrate bioequivalence between 1 and 5 mg tacrolimus capsules when administered as a 5 mg dose, i.e. five 1 mg capsules and one 5 mg capsule. FUSA will meet with FDA to discuss the protocol prior to initiation of the study.

8. **Please further define the lack of a role of bile in the absorption of tacrolimus.**

FUSA commits to evaluate the role of bile in the absorption of tacrolimus.

9. **Please evaluate the absorption of tacrolimus with respect to: i) various diet compositions; and ii) timing of food ingestion.**

FUSA commits to evaluate the absorption of tacrolimus with respect to: i) various diet compositions; and ii) timing of food ingestion. As FDA recognizes, this is a difficult area in which to conduct studies due to the severity of the medical condition of the patients and the large number of concomitant medications.

Fujisawa

10. Please submit for review on completion of the study the data being collected currently in your ongoing study to determine the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction.

FUSA agrees to conduct a study to confirm the pharmacokinetics of tacrolimus in patients with mild and severe hepatic dysfunction. Such a study has already been initiated and the protocol submitted to the NDA. FUSA commits to discuss this protocol further with FDA at the earliest opportunity.

11. Please determine the intra-subject variability of tacrolimus.

FUSA commits to perform additional analyses to determine the intra-subject variability of tacrolimus.

FUSA is committed to addressing these Phase IV requests to the best of our ability using current technology within the confines of conducting clinical research in transplant patients.

We hope these comments satisfactorily address the requests made by members of your Division. FUSA is committed to a sound scientific exploration of the attributes of tacrolimus.

At this time, we wish to commend the members of your Division responsible for the review of NDAs 50-708 and 50-709. They have demonstrated considerable flexibility and science-driven judgment in the evaluation of these NDAs. Our organization has enjoyed working with members of your Division and we hope to continue the partnership.

Please do not hesitate to contact the undersigned at (708) 317-8898 or Dr. Ramona E. Knaller at (708) 317-1396 if you have any questions or concerns.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson
Vice President, Regulatory Affairs

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015 2548
Tel. (708) 317-8800 • Telefax (708) 317-7296

Fujisawa

January 21, 1994

David W. Feigal, Jr., M.D., M.P.H., Director
Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Nicholson Research Center, 2nd Floor
5516 Nicholson Lane
Kensington, MD 20895

Re: NDA 50-708 PROGRAF™ (tacrolimus) Capsules
This Submission: CMC Amendment/Letter of Understanding

Dear Dr. Feigal:

This letter is written to confirm a verbal commitment made by Fujisawa USA, Inc. (FUSA) during a January 21, 1994 teleconference with members of your Division. FDA representatives at this teleconference were Drs. Mark Seggel and Chi Wan Chen. The FUSA representative was Dr. Ramona Krailler.

During this teleconference, FUSA agreed to withdraw from the NDA the blister packaging configuration for FK506 capsules. FUSA further agreed to modify the labelling to reflect the withdrawal of this packaging configuration (i.e., deletion of the appropriate information in the "How Supplied" section of the package insert).

FUSA will work with members of your Division to define the requirements for a supplement to provide for a unit dose blister packaging configuration of FK506 capsules. FUSA anticipates submitting such a supplement as soon as possible.

Thank you for the continuing opportunity to work with your Division.

Please contact me at (708) 317-8898 or Dr. Ramona Krailler at (708) 317-1396 if you have any questions or concerns.

Sincerely yours,

Jerry D. Johnson

Jerry D. Johnson, Ph.D
Vice President, Regulatory Affairs

DESK COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: November 30, 1990.
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa USA, Inc.	January 21, 1994
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
Parkway North Center 3 Parkway North Deerfield, IL 60015	(708) 317-8800
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA # 50-708

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Tacrolimus	Prograf

CODE NAME *(If any)*	CHEMICAL NAME
FK506, FK 506, FK-506, FR900506	[3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,monohydrate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Capsules	Oral	1mg, 5mg

PROPOSED INDICATIONS FOR USE

Prophylaxis of organ rejection in patients receiving allogeneic liver transplants and for treatment of refractory rejection.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND
IND
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DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☒ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314 50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)* Letter of Understanding

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Jerry D. Johnson, Ph.D. Vice President, Reg. Affairs	Jerry D. Johnson	1/21/94

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
3 Parkway North Deerfield, IL 60015	(708) 317-8898

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h (7/90)

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (708) 317-8800 • Telefax (708) 317-7286

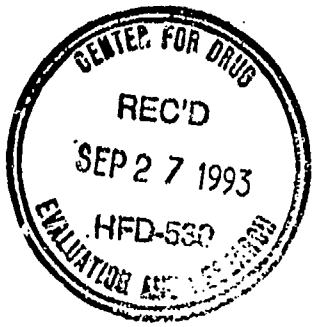
Fujisawa

DUPLICATE

September 24, 1993

David W. Feigal, Jr., M.D., M.P.H., Director
Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Nicholson Research Center, 2nd Floor
5516 Nicholson Lane
Kensington, MD 20895

NEW CORRESP
NC



Re: NDA 50-708, NDA 50-709
PROGRAF™ (tacrolimus) Capsules and Ampules
This Submission: Letter of Understanding

Dear Dr. Feigal:

This letter is written at the request of members of your Division to document the understanding reached between FDA and Fujisawa USA, Inc. (FUSA) during a September 24, 1993 teleconference. FDA representatives at this teleconference were Drs. Marc Cavaille-Coll and Donna Freeman and Ms. Carole Broadnax. FUSA representatives were Drs. Donald Buell, William Fitzsimmons, Ramona Krailler and James Shook.

During this teleconference, FUSA agreed to withdraw from the NDAs the indication for the treatment of

FUSA agreed to work with FDA to further modify the labelling to reflect the uncontrolled clinical experience with tacrolimus, as appropriate.

Thank you for the continuing opportunity to work with your Division.

Please continue to contact Dr. Ramona Krailler at (708) 317-1396 if you have any questions or concerns.

Respectfully yours,

Hatsuo Aoki, Ph.D.
Chairman and Chief Executive Officer, Fujisawa USA, Inc.
Managing Director, Fujisawa Pharmaceutical Co., Ltd.