CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-005

50-723/S-005

50-758/S-004

50-759/S-006

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	050722	**Trade Name:**	CELLCEPT (MYCOPHENOLATE MOFETIL) 250MG C
Supplement Number:	005	**Generic Name:**	MYCOPHENOLATE MOFETIL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	PROPHYLAXIS OF ORGAN REJECTION AND TREATMENT OF REFRACTORY ORGAN REJECTION IN PATIENTS RECEIVING ALLOGENEIC RENAL TRANSPLANTS
Action Date:	5/3/95		

Indication # 1 Prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants.

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	
2 months	16 years	Deferred	5/31/03

Comments: Pediatric liver studies have not been submitted (renal pharmacokinetic studies may be extrapolated). Related NDAs include 50-723/S-005, 50-758/S-004, and 50-759/S-006.

This page was completed based on information from Ellen Frank

/S/ 28 Jul 00

Signature - Ellen Frank Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	050723	**Trade Name:**	CELLCEPT (MYCOPHENOLATE MOFETIL) 500MG T
Supplement Number:	005	**Generic Name:**	MYCOPHENOLATE MOFETIL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	UN	**COMIS Indication:**	PROPHYLAXIS OF ORGAN REJECTION AND TREATMENT OF REFRACTORY ORGAN REJECTION IN PATIENTS RECEIVING ALLOGENEIC RENAL TRANSPLANTS
Action Date:	7/12/00		

Indication # 1 Prophylaxis of organ rejection in patients receiving allogeneic hepatic tranplants

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	
2 months	16 years	Deferred	5/31/03

Comments: Pediatric liver studies have not been submitted yet renal pharmacokinetic studies might be extrapolated to include these patients. Related NDAs include 50-722/S-005, 50-758/S-004, and 50-759/S-006.

This page was last edited on 9/6/00

Signature - Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	050758	**Trade Name:**	CELLCEPT (MYCOPHENOLATE MOFETIL HCL)PWD
Supplement Number:	004	**Generic Name:**	MYCOPHENOLATE MOFETIL HCL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	AP	**COMIS Indication:**	PROPHYLAXIS OF TRANSPLANT REJECTION AND INCREASED PATIENT AND GRAFT SURVIVAL IN PATIENTS RECEIVING ALLOGENIC RENAL TRANSPLANTS
Action Date:	7/28/00		

Indication # 1 Prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	
2 months	16 years	Deferred	5/31/03

Comments: Pediatric liver studies have not been submitted and renal pharmacokinetic studies might be extrapolated to include these patients. Related NDAs include 50-722/S-005, 50-723/S-005, and 50-759/S-006.

This page was last edited on 9/6/00

Signature - Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	050759	**Trade Name:**	CELLCEPT(MYCOPHENOLATE MOFETIL)200MG/ML
Supplement Number:	006	**Generic Name:**	MYCOPHENOLATE MOFETIL
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	UN	**COMIS Indication:**	PROPHYLAXIS OF TRANSPLANT REJECTION AND INCREASED PATIENT AND GRANT SURVIVAL IN PATIENTS RECEIVING ALLOGENIC RENAL TRANSPLANTS
Action Date:	7/12/00		

Indication # 1 Prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants
Label Adequacy: Adequate for SOME pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any):

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	
2 months	16 years	Deferred	5/31/03

Comments: Pediatric liver studies have not been submitted and renal pharmacokinetic studies might be extrapolated to include these patients. Related NDAs include 50-722/S-005, 50-723/S-005, and 50-758/S-004.

This page was last edited on 9/6/00

Signature · Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

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

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Syntex (U.S.A.) Inc.	October 1, 1999
TELEPHONE NO. *(Include Area Code)* (650) 354-2370	FACSIMILE (FAX) Number *(Include Area Code)* (650) 852-1861
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 3401 Hillview Avenue, Palo Alto, California 94303	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: Carmen R. Rodriguez, M.Sc., Regulatory Program Director, Tel: (650) 354-2370, Fax: (650) 852-1861

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): NDA 50-722

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mycophenolate Mofetil	CellCept

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexanoate

CODE NAME *(If any)*: RS-61443; Ro 106-1443/000

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsules	250 mg	oral

(PROPOSED) INDICATION(S) FOR USE:
Prophylaxis of organ rejection in patients receiving allogeneic renal or cardiac transplants

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b)(1) ☐ 505 (b)(2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application:

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D OCT 04 1999 CDR

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☑ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Clinical efficacy supplement (to NDA 50-722) for use in hepatic transplantation

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 55

THIS APPLICATION IS ☐ PAPER ☑ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

REC'D OCT 05 1999 EVALUATION AND RESEARCH

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please see attached list.

	This application contains the following items: *(Check all that apply)*
X	1. Index
X	2. Labeling (check one) ☑ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	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. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. 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.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carmen R. Rodriguez	Carmen R. Rodriguez, Regulatory Program Director	October 1, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3401 Hillview Avenue, Palo Alto, CA 94304	(650) 354-2370

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Date: January 21, 2000
Time: 2:15 p.m.
Location: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S440
Rockville, MD 20850

Application: NDA 50-722/S-005

Type of Meeting: Electronic Regulatory Submission Issues/Type C

Meeting Recorder: Matthew A. Bacho, Regulatory Project Manager

FDA Attendees, titles, and Office/Division:
Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Joyce A. Korvick, M.D., Medical Officer and Meeting Chairperson
Rigoberto Roca, M.D., Medical Officer
Mike Elashoff, Ph.D., Statistics Acting Team Leader
Karen Higgins, Sc.D., Statistics Reviewer
Matthew A. Bacho, Regulatory Project Manager

External Constituent Attendees and titles:
Eleanor Ramos, M.D., Medical Director
Carmen Rodriguez, M.Sc., Regulatory Program Director
Mercidita Navarro, Ph.D., Senior Statistician
Sabine Geisel, Ph.D., Senior Regulatory Program Manager
Whedy Wang, Ph.D., Senior Statistician

Background: Hoffman-La Roche requested, and was granted, a teleconference to discuss the electronic regulatory submissions (ERS) for their supplemental NDA for CellCept® in liver transplant recipients and an upcoming pediatric use supplement for the same drug product.

Meeting Objective: The FDA sought changes to the ERS for the liver supplement to facilitate the ongoing review of that application, and it was anticipated that these modifications could be used to improve the ERS for the upcoming pediatric use supplement.

Discussion Points:

[Note: The discussion points in bold typeface were taken from correspondence that was sent to Roche on January 20, 2000, by the Agency.]

1. **Please check your adverse events file and correct the categories under severity. Specifically, only one code should be entered in each column: either grade the**

events using the scale from one to five or use mild, moderate, severe, life threatening, and fatal to describe the events. Both a numeric scale of 1 - 4 and a descriptive scale of mild, moderate, severe, and fatal are used in the same column, which makes the data difficult to interpret.

Roche noted that the adverse event files contains both adverse events and opportunistic infections. One was graded using a numerical scale, while the other used a descriptive scale. Roche agreed to resubmit the file using the descriptive scale only for the description of severity.

2. **According to the guidance for electronic submissions, the SAS transport files should be no larger than 25 MB. All of the laboratory data files (1, 2 and 3) exceed this size, making them unusable to the primary reviewers through the JMP software.**

   Roche agreed to reorganize the SAS laboratory data files by physiologic group to reduce their size.

3. **In addition, while it is acceptable to provide more than one file for laboratory data, we would like to propose organizing these files according to physiologic groups, which would make the data easier to review. For example, one file could contain all of the liver function data for all of the patients in the study (with separate files on kidney function, hematology, electrolytes, etc.). We look forward to speaking with you about reformatting these safety data files.**

   Roche agreed to follow this suggestion instead of organizing the data by investigator; however, if these groupings should generate files larger than 25 MB in size then another scheme should be used. *The FDA noted that the liver function tests file should contain aspartate transaminase, alanine transaminase, and bilirubin. The hematology file would encompass white blood cell, basophil, eosinophil, granulocyte, and neutrophil counts. The renal function tests would be placed in their own table and a miscellaneous file would contain laboratory values that aren't easily categorized (e.g., amylase). All of these data should be organized in ascending order using the date and patient identification. The Agency also noted that the rest of the ERS for the liver supplement met its needs.*

4. **Finally, please provide the histologic grade for each episode of biopsy-proven acute rejection.**

   Roche assured the FDA that the revised efficacy datasets would include this additional variable.

5. In terms of the upcoming (February 18, 2000) pediatric use supplement for CellCept®, Roche noted that they would incorporate the suggestions outlined above. There would not be a reviewers' aid, all of the patient listings for Section 11 of the supplemental NDA would be submitted in PDF (portable document file) format, and all of the SAS transport files would be archivable. Roche also confirmed that Adobe

Acrobat 4.0 would be used in creating all of the PDF files. *The FDA noted that all text files (e.g., final study reports and integrated summaries) could no longer be accepted in Microsoft Word, making PDF the only format available for these documents.*

Roche acknowledged this statement.

Action Items:

Roche will reorganize, as mentioned above, the efficacy, laboratory data, and adverse event files of the liver supplement for CellCept® (NDA 50-722/S-005) and submit them for review.

Minutes Preparer: /S/ 3/9/00

Meeting Chairperson: /S/ 3/8/00

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation IV/ Division of Special Pathogens and Immunologic Drug Products

DATE: July 27, 2000

TO: Renata Albrecht, M.D.
Acting Division Director, HFD-590

FROM: Marc W. Cavaillé-Coll, M.D., Ph.D. 7/27/00
Medical Officer Medical Team Leader, HFD-590

SUBJECT: NDA 50-722/S-005, CellCept® (mycophenolate mofetil) for the prophylaxis of organ rejection in allogeneic liver transplantation.

The major issues of this efficacy supplement have been thoroughly discussed in the pre-clinical,statistical and clinical reviews. I concur with the consensus of the reviewers that CellCept® (mycophenolate mofetil) used concomitantly with cyclosporine and corticosteroids, should be approved for the indication of prophylaxis of organ rejection in patients receiving allogeneic liver transplants, to be. This memorandum will briefly comment on a few areas that have been discussed at some length during the review process.

CellCept® is approved for the prevention of graft rejection in allogeneic kidney or heart transplantation, and is used in combination with cyclosporine and corticosteroids. The recommended initial dose in kidney transplantation is 1gram bid and 1.5 gram bid in heart transplantation. The dose chosen for the phase III evaluation of the safety and efficacy of CellCept® in liver transplantation was 1.5 gram bid, based on pharmacokinetic information, supporting that this dose would produce blood concentrations similar to those produced by 1 gram bid in renal transplant recipients.

This efficacy supplement is supported by a single large phase III, double-blind randomized, controlled study that enrolled 565 subjects in 22 clinical centers in the United States, Europe, Canada and Australia, and compared MMF at an initial dose of 1.5 gram bid to an active control, azathioprine. Azthioprine is not approved for the prevention of graft rejection in liver transplantation, and an optimal safe and effective dose has not been established for this indication. While the recommended dose of azathioprine in the written protocol was 1-2 mg/kg per day, the median average daily dose administered was 1.29 mg/kg and 1.26 mg/kg during the first 6 and 12 months on study, respectively. This appears to be on the lower end of what has been used in other clinical trials in liver transplantation. Thus, comparisons between MMF and azathioprine in this clinical trial should be interpreted with caution. Nevertheless, there was a lower rate of treatment failure at six months, defined as acute rejection, graft loss or death, among patients assigned to MMF compared to those assigned to azathioprine, which is

sufficiently convincing that CellCept® would have been found superior to a placebo control. It should be noted that one of the strengths of the study design was the masking of the treatment assignment, which helped protect the assessment of biopsy proven rejection endpoints from potential sources of bias.

Another strength of this study was an almost complete assessment of patient and graft survival endpoints at 12 months. Only two patients were lost to follow up at 12 months and were considered as treatment failures in the primary analysis. Patient and graft survival at 12 months were comparable across treatment groups, suggesting that a lower rate of rejection was not obtained at the expense of an unacceptable increase in patient death or graft loss. Conversely, a higher rate of rejection at 6 months in the azathioprine arm was not associated with a detectable increase in patient or graft loss at 12 months. Nor was the use of additional corticosteroids to treat rejection in the azathioprine treatment group associated with a detectable increase in steroid-related morbidity. Overall, the long-term prognostic value of a single episode of acute rejection is uncertain in liver transplantation. However, because of the high rate of premature discontinuation of study drug at 12 months across both treatment arms (greater than 50%), analyses of equivalence should be interpreted with caution.

Tacrolimus (Prograf®), which is approved for the prevention of allogeneic graft rejection in liver transplantation when used with corticosteroids, was used instead of cyclosporine in a small subset of subjects. However, the number of subjects was too small to meaningfully evaluate the efficacy and safety of this combination or its relative contribution to outcomes at 6 and 12 months. Some preliminary clinical information on the effect of MMF on whole blood levels of tacrolimus was included in this supplement, but there were insufficient data on the safety and efficacy to warrant inclusion of experience with this unapproved combination in the proposed package insert.

One of the weaknesses of this supplemental application is the paucity of information on the use of CellCept® in pediatric liver transplant recipients, aged less than 18 years who represent approximately 15% of liver transplant recipients in the US, 2/3rd of whom are less than 6 years old. Biliary atresia is the most common cause of liver failure in young children leading to liver transplantation. Thus, the applicant has been requested to include the evaluation of the pharmacokinetics and safety of CellCept® in pediatric liver transplant recipients (including infants transplanted because of biliary atresia) during phase 4 development (see phase 4 commitments). The requirement for pediatric information is being deferred until 2003.

Another weakness of this supplemental application is the lack of sufficient numbers of African American liver transplant recipients to evaluate potential racial differences in pharmacokinetics and safety. The applicant has committed to address this in phase 4 (see phase 4 commitments).

There remains a need for a better understanding of the long-term outcome of treatment with CellCept® in liver transplantation. The phase 3 clinical study supporting this application, was masked until the last enrolled subject had completed 12 months on study. After this time, patients will continue to be followed through a total of 3 years. Information on long-term

follow-up will be collected and reported to the Agency as part of phase 4 development (see phase 4 commitments).

During the postmarketing experience of this product, rare cases of interstitial lung disorders, including fatal pulmonary fibrosis have been reported in transplant recipients receiving CellCept®.. Based on cases reviewed in 1998 and 2000 OPDRA recommended that these events be added to the labeling. After review of additional materials submitted by the applicant on July 18, 2000, it was agreed during a telephone conference, on July 26, 2000, to add wording on interstitial pulmonary events in the **Postmarketing Experience** section of the label under **ADVERSE REACTIONS**.

Finally, CellCept® represents the first new immunosuppressant for prevention of graft rejection in liver transplantation to be approved since 1994, and should be considered a welcome addition to the limited number of available agents approved for this indication.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: January 20, 2000

TO: Carmen Rodriguez, M.Sc.
Regulatory Program Director
Roche Pharmaceuticals
(650) 354-2370
(650) 855-5589 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Joyce A. Korvick, M.D., Medical Officer
Karen Higgins, Sc.D., Statistics Reviewer

NDA: NDA 50-722/S-005 (CellCept®)

SUBJECT: Comments regarding the Electronic Regulatory Submission

With reference to your supplemental new drug application for the use of CellCept® to prevent organ rejection in patients receiving allogeneic hepatic transplants and in anticipation of our teleconference on January 21, 2000, our reviewing medical officer and statistician have a few comments:

1) Please check your adverse events file and correct the categories under severity. Specifically, only one code should be entered in each column: either grade the events using the scale from one to five or use mild, moderate, severe, life threatening, and fatal to describe the events. Both a numeric scale of 1 - 4 and a descriptive scale of mild, moderate, severe, and fatal are used in same column, which makes the data difficult to interpret.

2) According to the guidance for electronic submissions, the SAS transport files should be no larger than 25 MB. All of the laboratory data files (1, 2 and 3) exceed this size, making them unusable to the primary reviewers through the JMP software.

3) In addition, while it is acceptable to provide more than one file for laboratory data, we would like to propose organizing these files according to physiologic groups, which would make the data easier to review. For example, one file could contain all of the liver function data for all of the patients in the study (with separate files on kidney function, hematology, electrolytes, etc.). We look forward to speaking with you about reformatting these safety data files.

4) Finally, please provide the histologic grade for each episode of biopsy-proven acute rejection.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Bacho

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: March 13, 2000

TO: Carmen Rodriguez, M.Sc.
Regulatory Program Director
Roche Pharmaceuticals
(650) 354-2370
(650) 852-1861 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Joyce A. Korvick, M.D., Medical Officer
Rigoberto Roca, M.D., Medical Officer
Karen Higgins, Sc.D., Statistics Reviewer

NDA: NDA 50-722/S-005 (CellCept®)

SUBJECT: Request for Information

With reference to your supplemental new drug application for the use of CellCept® to prevent organ rejection in patients receiving allogeneic hepatic transplants, our reviewing medical officers and statistician request the following information:

> On page 144 of volume 17, a summary table (#6) describing the key baseline characteristics of liver allografts was provided for our review. We would like to see the individual patient data submitted for Primary Cause of Hepatic Failure, CMV Serologic Status for Donor and Recipient, and Hepatitis B Serologic Status for Donor and Recipient as a SAS transport file, the source for which, as noted at the bottom of table, was "RMMD TBASELIN (20MAY99 10:57) TBASELIN.TAB."

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

BACHO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE:	April 13, 2000
TO:	Carmen Rodriguez, M.Sc. Regulatory Program Director Roche Pharmaceuticals (650) 354-2370 (650) 852-1861 (fax)
FROM:	Matthew A. Bacho, Regulatory Project Manager
THROUGH:	Joyce A. Korvick, M.D., M.P.H., Medical Officer Kofi A. Kumi, Ph.D., Clin. Pharm. & Biopharmaceutics Reviewer
NDA:	NDA 50-722/S-007 (CellCept®)
SUBJECT:	Request for Information

With reference to your supplemental new drug application for the use of CellCept® to prevent organ rejection in pediatric patients receiving allogeneic renal transplants, our reviewing medical officer and clinical pharmacologist request the following information:

1) Please provide us with the date of submission and location within the supplemental NDA of the pilot study MYC2190.
2) Could you provide the meaning behind "Master Reference Number" and whether we can use this information to locate specific pieces of information?
3) Please send a data set that includes the outcome/efficacy of CellCept® in pediatric kidney transplant patients in study MYCS2675. Review of the current SAS transport sets does not reveal an "efficacy" file. Although this study is not powered to describe the efficacy of CellCept® in pediatric patients, it is important for us to review outcomes to ensure that the rejection rates are no worse that that which would be expected in this group of patients.
4) Finally, we determined that NDA 50-722/S-007 was fileable.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: June 20, 2000

TO: Carmen Rodriguez, M.Sc.
Regulatory Program Director
Hoffman-La Roche Inc.
(650) 354-2370
(650) 852-1861 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Joyce A. Korvick, M.D., M.P.H., Medical Officer
Rigoberto Roca, M.D., Medical Officer
Karen Higgins, Sc.D., Acting Statistics Team Leader

NDAs: 50-722/S-005 (CellCept® Capsules)
50-758/S-004 (CellCept® Intravenous)

SUBJECT: Request for Information

During the review of your supplemental NDAs for the use of CellCept® in the prevention of acute rejection in liver transplant recipients, our medical officer and statistician noticed that the rationale provided for the choice of the control drug (azathioprine) and its dose were not as detailed as they could have been. As with the cardiac transplant indication, because azathioprine is only labeled for kidney transplantation, more detail is requested.

1) Please supply a rationale that includes references to dosages that are commonly utilized and the approximate rejection rates that occurred at these doses in the "standard regimen." We acknowledge that you have a rationale section in the application; however, this should be extended.

2) Please perform an analysis using logistic regression to determine the relationship between the average dose of azathioprine in the first month to the six-month acute rejection endpoint in the patients randomized to azathioprine.

We believe the answer to these requests will strengthen the application and help to explain the difference between the rejection rates at 6 months and the survival rates at 12 months.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE

DATE: July 27, 2000

TO: Carmen Rodriguez, M.Sc.
Regulatory Program Director
Roche Pharmaceuticals
(650) 354-2370
(650) 852-1861 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Joyce A. Korvick, M.D., M.P.H., Medical Officer
Rigoberto Roca, M.D., Medical Officer Team Leader

NDAs: 50-722/S-005 (CellCept® Capsules)
50-723/S-005 (CellCept® Tablets)
50-758/S-004 (CellCept® Intravenous)
50-759/S-006 (CellCept® Oral Solution)

SUBJECT: Phase 4 Commitments

With reference to your supplemental new drug applications for the use of CellCept® to prevent organ rejection in patients receiving allogeneic hepatic transplants and the teleconference we had on July 26, 2000, we would like to recommend the following Phase 4 commitments:

1) You will collect and report 3-year, follow-up safety and efficacy data from the ongoing Phase 3 Study MYCS2646, whether or not patients remain on study drug.

2) You will conduct an appropriate study or studies on the pharmacokinetics and safety of CellCept® in African American liver transplant recipients.

3) You will conduct an appropriate study or studies on the pharmacokinetics and safety of CellCept® in very young (less than 12 years old) liver transplant recipients, especially infants (less than 3 years old) with biliary atresia.

If these are acceptable to you, please submit your acknowledgement and commitments to the efficacy supplements listed above. If you require more discussion with the Division, please contact us as soon as possible and we will schedule a teleconference to take care of your concerns.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

/S/
Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products