

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 050759

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Roche

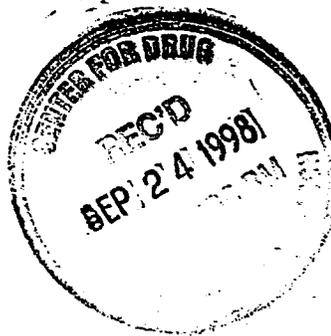
Pharmaceuticals

ORIGINAL
NEW CORRESPONDENCE

September 22, 1998

NC
Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852

Re: NDA 50-759
CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
Proposal for Final Labeling



Dear Reviewers:

Ms. Dempsey informed us today by phone that we are asked to add the statement "Do not freeze." to the package insert and the bottle and carton labels.

We agree with this proposal. Please find attached the revised proposed package insert. We have added the statement to sections Dosage and Administration: Preparation of Suspension (p. 30 of the package insert) and How supplied: (p. 33 of the package insert). In addition, we have also corrected a mistake in table Pharmacokinetic Parameters for MPA (p. 5 of the package insert) where the information "(n=31)" has been left out in the last column. A diskette with the proposed label in revision mode is also provided for your convenience.

We will also add the statement "Do not freeze." to the bottle and carton labels. These changes will be made to the final bottle and carton labels, which will be submitted to you at a later point in time.

Please do not hesitate to contact either me at (650) 855-5923 or Mrs. Carmen Rodriguez at (650) 354-2370 should you require additional information.

*nk for
S. Geisel*

Sincerely,

Dr. Sabine Geisel
Regulatory Program Manager

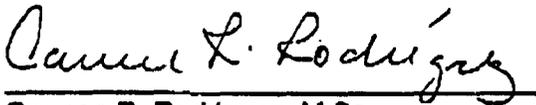
FDA: (2) copies
Desk copies (1): for Ms Mary Dempsey
via: Federal Express

NDA 50-759

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

Certification Statement for Generic Drug Enforcement Act of 1992

On behalf of Syntex (U.S.A.) Inc., Roche Global Development has made a diligent effort to insure that no person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act has provided any services in connection with this application. Relying on this effort, Roche certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
Regulatory Agent for Syntex (U.S.A.) Inc.

APPEARS THIS
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL



PATENT INFORMATION

MYCOPHENOLATE MOFETIL is the subject of US patents 4,753,935 and 4,786,637.

The Patent Information which is attached refers to CellCept® Oral Suspension (mycophenolate mofetil) Powder for Suspension, 200 mg/mL, NDA 20-858. We received notice from the FDA subsequent to the issuance of the patent information that the name and NDA number for this drug have been changed. The name and NDA number as agreed to with the FDA are: CellCept® Oral Suspension (mycophenolate mofetil for oral suspension), 200 mg/mL, NDA 50-759.

Attached please find the Patent Declaration and all relevant information about these patents.

**APPEARS THIS WAY
ON ORIGINAL**

PATENT INFORMATION

CellCept® Oral Suspension (mycophenolate mofetil) Powder for Oral Suspension, 200 mg/mL
NDA 20-858

Syntex (U.S.A.) Inc. submits the following patent information, as required by 21 U.S.C. 355(b) and in compliance with 21 CFR 314.53(c) and the notice at 62 FR 22216.

The following patents are relevant to this New Drug Application:

Patent No. 4,753,935; expires May 3, 2009;	drug,
Patent No. 4,786,637; expires January 30, 2007;	drug product,
	method of use;

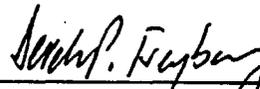
The owner of the patents is:

Syntex (U.S.A.) Inc.
3401 Hillview Avenue
Palo Alto, California 94304

DECLARATION

The undersigned declares that U.S. Patents Nos. 4,753,935 and 4,786,637 cover the formulation, composition, and/or method of use of CellCept® Oral Suspension (mycophenolate mofetil) Powder for Oral Suspension, 200 mg/mL. This product is the subject of this application for which approval is being sought.

APPEARS THIS WAY
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Derek P. Freyberg

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 50-759 SUPPL # _____

Trade Name Cellcept Oral Suspension Generic Name mycophenolate mofetil for oral suspension
Applicant Name ROCHE HFD-590

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA? *Submitted under 507 'old antibiotic'*
YES / / NO / ___ /

b) Is it an effectiveness supplement?
YES / ___ / NO / ___ /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES / ___ / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

**APPEARS THIS WAY
ON ORIGINAL**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

**APPEARS THIS WAY
ON ORIGINAL**

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

**APPEARS THIS WAY
ON ORIGINAL**

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES / ___ /! NO / ___ / Explain: _____

Investigation #2

IND # ____ YES / ___ / NO / ___ / Explain: _____

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

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Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ / NO / ___ /

If yes, explain: _____

IS/
Signature
9/25/98
Date

Project Manager
Title

IS/
Signature of Division Director
10/1/98
Date

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 50-758
HFD-590/Division File
HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 50-759 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-590 Trade and generic names/dosage form: Cipro[®] Oral Suspension (mycophenolate mofetil for suspension)
Action: AP AE NA

Applicant Roche Global Development Therapeutic Class 3S Innumosupressant
Indication(s) previously approved Prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in patients receiving allogeneic cardiac transplants.
Pediatric information in labeling of approved indication(s) is adequate inadequate _____
Indication proposed in this application Prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in patients receiving allogeneic cardiac transplants.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) ___ No (Sign and return the form)
IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ___ Children (2-12yrs) ___ Adolescents(12-16yrs)

- ___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- ___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- ___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - ___ c. The applicant has committed to doing such studies as will be required.
 - ___ (1) Studies are ongoing,
 - ___ (2) Protocols were submitted and approved.
 - ___ (3) Protocols were submitted and are under review.
 - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
 - ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- ___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary. Safety and effectiveness in pediatric patients have not been established. Very limited pharmacokinetic data are available in pediatric patients.
ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

/S/

Mary Dempsey, Project Manager
Signature of Preparer and Title

September 29, 1998
Date

Orig NDA/BLA # 50-759
HFD-590/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

ORIGINAL



Pharmaceuticals

January 6, 1998

BC

ORIG AMENDMENT

Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20850



Re: Environmental Assessment Report - Application for Categorical Exclusion
NDA 50-759 CellCept Oral Suspension

Dear Reviewers:

As requested by Dr. Mark Seggel and in accordance with the revised regulations governing compliance with the National Environmental Policy Act (published in the Federal Register on July 29, 1997) Roche would herewith like to apply for a categorical exclusion for submitting an environmental assessment report for NDA 50-759. The present request is in compliance with the categorical exclusion criteria established by 21 CFR §25.31(b) and we state that to our knowledge no extraordinary circumstances exist (21 CFR §25.21).

Should you require any additional information, please do not hesitate to contact either me by phone at (650) 354-2370 or fax at (650) 852-1861 or Dr. Sabine Geisel by phone at (650) 855-5923.

Sincerely,

Carmen R. Rodriguez
Carmen R. Rodriguez, M.Sc.
Regulatory Program Director

cc: Dr. Mark Seggel

Copies (5): Attn. Ms. Lisa Hubbard
via: Federal Express

Global Development-Palo Alto
a Division of Syntex (U.S.A.) Inc.

3401 Hillview Avenue
Palo Alto
California 94304-1397

Phone: (415) 855-5050

ORIGINAL



Pharmaceuticals

September 17, 1998

NDA ORIG AMENDMENT

N/BC

Division of Special Pathogens and Immunological Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852



Re: NDA 50-759 CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
Response to CMC Questions Received on August 28, 1998 by Phone
here: - Submission of Revised Specifications (as addressed in our letter of 9/9/1998)
- Submission of DMF Authorization letters and Manufacturer's Certificate of
Analysis (as clarified in Dr. Seggel's voice mail of 9/16/1998)

Dear Reviewers:

Please find attached revised specifications and directions for testing for the finished product CellCept Oral Suspension as addressed in our letter of September 9, 1998.

As agreed in our letter of September 9, 1998 a test
has been added to the product specifications.

In addition, the following revisions have been made to the finished product specifications:

- A test for according to USP has been added.
- Directions for testing for suspension have been added.
- The methodology to determine has been revised to use an instead of a The data read development laboratory and the Roche commercial laboratory were more comparable when both sites used
- The note for procedure to constitute the suspension (page 2 of 25 of the finished product specifications and directions for testing) has been modified to allow the suspension to stand overnight prior to use in the analyses to better accommodate the workflow in the laboratory.

As clarified in Dr. Seggel's voice mail of September 16, 1998, please also find attached the authorization letters for

- Drug Master File
- Drug Master File

Finally, we also included copies of the manufacturer's certificate of analysis for
Please note that we were only able to receive a faxed copy of
the certificate of analysis for We will provide you with a
better copy as soon as possible.

We thank you for your support of the CellCept program. In case you need any further information regarding this submission, please do not hesitate to contact me by phone at (650) 855-5923 or by fax at (650) 852-1861 or Mrs. Carmen Rodriguez by phone at (650) 354-2370.

Sincerely,



Sabine Geisel, Ph.D.
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

FDA: (2) copies
Desk copies: (1) for Ms Mary Dempsey
via: Federal Express

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Reviewed
9/28/98

DC



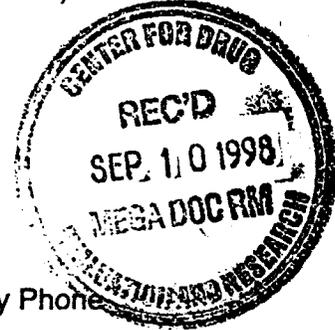
/S/

ORIG ATTACHMENT

DUPLICATE

September 9, 1998

Division of Special Pathogens and Immunological Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852



Pharmaceuticals

Re: NDA 50-759 CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
- Response to CMC Questions Received on August 28, 1998 by Phone
- Submission of Updated Package Insert

Dear Reviewers:

Please find attached our responses to the CMC questions for CellCept Oral Suspension (NDA 50-759) which we received on August 28, 1998 by phone.

Please also find attached the updated proposed package insert for CellCept Oral Suspension (Attachment 5). This update is based on the latest approved package insert for CellCept, including the indication for cardiac transplantation and the new intravenous dosage form, CellCept Intravenous. The information that relates to suspension or is changed compared to the currently approved CellCept label is marked in revision mode.

The information included is the same as originally submitted to FDA on September 30, 1997, with the following exceptions:

- The information
- The wording for the storage recommendations has been changed to be in line with the wording for CellCept capsules, tablets and CellCept Intravenous.
The proposed wording is:

The stability data supporting the storage of the constituted suspension in a refrigerator are included in the first addendum to the stability report for mycophenolate mofetil powder for oral suspension. This addendum has been submitted to NDA 50-759 on March 6, 1998.

- The first sentence in section Handling and Disposal has slightly been changed for grammatical reasons.

A diskette with the proposed label in revision mode is also provided for your convenience.

Attachment 6 contains full color mock-ups with the revised text for the carton and bottle label. The revisions reflect the removal of the colorants and the changed wording for the storage recommendations. In addition, the caution statement has been replaced with the statement "Rx only" in accordance with the FDAMA guidelines.

We thank you for your continued support of the CellCept program. In case you have any further questions regarding this submission, please do not hesitate to contact me by phone at (650) 855-5923 or by fax at (650) 852-1861 or Mrs. Carmen Rodriguez by phone at (650) 354-2370.

Sincerely,



Sabine Geisel, Ph.D.
Regulatory Program Manager

**APPEARS THIS WAY
ON ORIGINAL**

FDA: (2) copies
Desk copies: (5) for Ms Mary Dempsey
via: Federal Express

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ORIGINAL



Pharmaceuticals

May 29, 1998

Mr. Nicholas Falcone
Food and Drug Administration
2nd and Chestnut Streets
Custom's House Room 900
Philadelphia, PA 19106-2973



Re: NDA 50-759: CellCept® Powder for Oral Suspension
Submission of samples for method validation studies

Dear Mr. Falcone, _

As requested in your faxed letter of May 19, 1998 and as discussed in our conversation on May 26, 1998 we are hereby providing the following samples and materials for method validation studies for CellCept® Powder for Oral Suspension:

I. Materials

- Reference Standard - Mycophenolate Mofetil
- Reference Standard
- Reference Standard for

- Finished Product: CellCept® Powder for Oral Suspension

As agreed in our phone call of May 26, 1998, we are including only 10 mg of the sorbitol ester of mycophenolic acid, but we will be happy to provide additional substance upon request at a later time.

II. Certificates of Analysis

- Certificate of Analysis for Mycophenolate Mofetil reference standard (Lot E6-NF-017)
- Certificate of Analysis for
- Certificate of Analysis for
- Certificate of Analysis for CellCept® Powder for Oral Suspension (Lot 61443-000-1547891)

Stability testing results at 11.7 months for CellCept® Oral Suspension (Lot 61443-000-1547891) are also included.

III. MSDS

- MSDS for Mycophenolate Mofetil

IV. Directions for Testing

The latest version of the Directions for Testing (DFTs), which includes the methods and specifications, is included in this submission. This revision, submitted to the FDA on May 12, 1998

An earlier revision was submitted to the FDA on February 13, 1998.

In addition, please note that the Central File Number for the manufacturing site (Hoffman-LaRoche Inc, Nutley, NJ) is

We greatly appreciate your cooperation in assisting Roche to pursue the approval of the CellCept® Powder for Oral Suspension application.

Please do not hesitate to contact me by phone at (650) 855-5923 or fax at (650) 852-1861 or Ms. Carmen R. Rodriguez at (650) 354-2370 should you require additional information or clarification.

Sincerely,

Alice M. Varga
for

Sabine Geisel, Ph.D.
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The following information is provided for performing method validation studies on CellCept (mycophenolate mofetil) for Oral Suspension in connection with NDA 50-759.

1. *Directions for Testing*
2. A) Certificate of analysis for Cellcept for Oral Suspension lot 61443-000-1547891
B) Stability results for lot 61443-000-1547891 at 11.7 months, 25°C/60%RH
3. Certificate of analysis for reference standards:
A) Mycophenolate mofetil
4. Material safety data sheets for:
A) Mycophenolate mofetil
5. Worksheets, sample calculations, and mycophenolate mofetil
6. Worksheets, sample calculations, and
7. Worksheets and testing for units initial release

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ON ORIGINAL

BC

ORIG AMENDMENT
ORIGINAL



Pharmaceuticals

May 12, 1998

Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852

Re: NDA 50-759 - CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
Revised Specifications and Test Methods



Dear Reviewers:

During the on-going pre-approval inspection for NDA 50-759 for CellCept Oral Suspension (mycophenolate mofetil for oral suspension) at the Hoffmann-La Roche, Nutley, New Jersey facility the FDA inspector and the company agreed to revise the specifications for mycophenolate mofetil (MMF) content filed with the NDA.

In addition

will be This
recommendation was based on review of all available information, which includes additional stability data (up to 12 months), a data and further
review of the manufacturing capabilities. The proposed revisions are fully supported by an optimized manufacturing process.

Enclosed herein you will find the following documents:

1. A copy of the signed revised specifications and method of testing for CellCept Oral Suspension.
2. A report describing the revisions to the specifications, including the rationale for the changes, with an attachment describing the optimization of the manufacturing process.

A copy of the revised specifications and methods of testing and the justification for the changes has been submitted to Mr. Matthew Spataro, Investigator of the FDA - New Jersey District on May 11, 1998.

We would like to discuss the proposed revisions with Dr. Seggel in a teleconference. We would like to propose to have this teleconference on Friday, May 15, 1998. We will contact Ms. Mary Dempsey shortly to confirm a mutually convenient time for this interaction.

ORIGINAL



Pharmaceuticals

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ORIG AMENDMENT

March 6, 1998

Division of Special Pathogens and Immunologic Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852

Re: NDA 50-759 - CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
Submission of additional stability data



Dear Reviewers:

We are hereby submitting an addendum to the report for the stability studies of mycophenolate mofetil for oral suspension. This addendum provides 12- month stability data for the three primary stability batches and 17-month data of the batch used in the bioequivalence study. It also includes 2- and 3-month stability data for the constituted suspension stored at 5°C and 30°C/60%RH.

Thank you for your continued support of the development program for mycophenolate mofetil. In case you have any further questions regarding this submission, please either contact Mrs. Carmen Rodriguez by phone at (650) 354-2370 or by fax at (650) 852-1861 or me by phone at (650) 855-5923.

Sincerely,

Sabine Geisel, Ph.D.
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

via: Federal Express
Desk Copies (3) Ms Lisa Hubbard

ORIGINAL

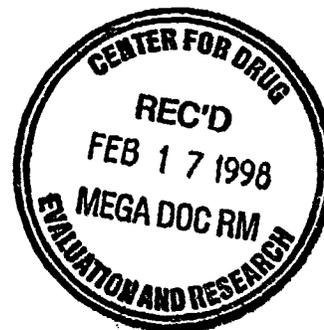


Pharmaceuticals

February 13, 1998

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20850

Handwritten initials and date: MAY 10 1998



Handwritten: ONE AMENDMENT

Re: NDA 50-759
CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
Updates to the CMC portion of the submission

Dear Reviewers:

Reference is made to the letter of January 22, 1998 in which Roche Global Development requested a teleconference to discuss formulation for CellCept Oral® Suspension submitted as part of NDA 50-759 on September 30, 1997. We also refer to a subsequent telecommunication (January 27, 1998) between Ms Carmen Rodriguez and Ms Lisa Hubbard in which Ms Hubbard explained that no teleconference would be needed to discuss this matter and mutual agreement was reached to submit updated CMC documents reflecting the removal of these colorants to NDA 50-759. Roche is herein submitting those revised CMC documents. A copy of the original Table of Contents of the CMC section of NDA 50-759 is attached; revised documents have been highlighted for the convenience of the reviewer.

In addition, a revised version of the description of the Container-Closure System is included. This revised version includes description

The revised document now includes it for completeness.

We thank you for your continued support for the CellCept® Oral Suspension NDA. Please do not hesitate to contact me at (650) 855-5923 or Ms Carmen Rodriguez at (650) 354-2370 should you require additional information or clarification.

Sincerely,
Alice M. Varga
for

Dr. Sabine Geisel
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

Desk copies: (3): for Ms. Hubbard
via Federal Express

Global Development-Palo Alto
a Division of Syntex (U.S.A.) Inc.

3401 Hillview Avenue
Palo Alto
California 94304-1397

Phone: (415) 855-5050

Pharmaceuticals



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3/27/98

January 22, 1998

Division of Special Pathogens and Immunological Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852

NC
NEW ORAL SUSP



Re: CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)
NDA 50-759 - Background information for teleconference (planned for January 26, 1998)

Dear Reviewers:

A dossier for CellCept® Oral Suspension was submitted on September 30, 1997 in the US (New Drug Application, NDA 50-759) as well as in Europe (Application for Marketing Authorization in the Centralized Procedure).

Therefore, our rapporteur in the centralized procedure, the U.K., recommended in the assessment report of November 27, 1997

At this point the company decided to

In a teleconference (planned for January 26, 1998, to be confirmed by Ms. Hubbard) we would like to discuss this issue with the CMC reviewer especially with regard to documentation of the planned change in the US and the best time for submission of this material to the FDA.

We thank you for your continued support and look forward to a productive teleconference. Please do not hesitate to contact either contact Mrs. Carmen Rodriguez at (650) 354-2370 or me at (650) 855-5923 should you require additional information or clarification.

Sincerely,

S. Geisel
Dr. Sabine Geisel
Regulatory Program Manager

Desk copies (3): att. Ms. Hubbard
via: Federal Express

NC
NEW CORRESP
COPY



NIAI
7/16/98
/S/

October 17, 1997

Division of Special Pathogens and Immunological Drug Products (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20852



Pharmaceuticals

Re: NDA 50-759 - Electronic files of CMC documents
CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)

Dear Reviewers:

Please find attached electronic files of the key CMC documents originally included in the paper NDA for CellCept® Oral Suspension (NDA 50,759) submitted on September 30, 1997.

The attached optical disk contains the documents listed in the Directory of Electronic Files provided with this submission. All documents are formatted as pdf files. This format will allow reviewers to use all Acrobat® Reader features. An instruction sheet for viewing the files is also provided. In addition, most documents are also provided in Microsoft Word (Version 6.0 for Windows) and may be opened directly from the pdf files. To further facilitate the review all the stability tables are provided as Microsoft Excel Version 5.0 spreadsheets, which can also be opened directly from the pdf files.

We trust these electronic files will be a useful tool to reviewers. We look forward to working with you during the review of this NDA. In case you have any further questions regarding this submission, please either contact Mrs. Carmen Rodriguez at (650) 354-2370 or me at (650) 855-5923.

Sincerely,

Dr. Sabine Geisel
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

Enclosures: CD-ROM
Directory of Electronic Files
Instructions for Viewing the Electronic Files

via: Federal Express



NDA 50-759

Food and Drug Administration
Rockville MD 20857
CERTIFIED MAIL
RETURN RECEIPT

Roche Global Development
Attention: Carmen Rodriguez, M.Sc.
3401 Hillview Avenue
Palo Alto, CA 94304-1397

OCT 27 1997

Dear Ms. Rodriguez:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: CellCept Oral Suspension

Therapeutic Classification: Standard

Date of Application: September 30, 1997

Date of Receipt: October 1, 1997

Our Reference Number: 50-759

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 1, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Lisa Hubbard, Regulatory Management Officer, at (301) 827-2416.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

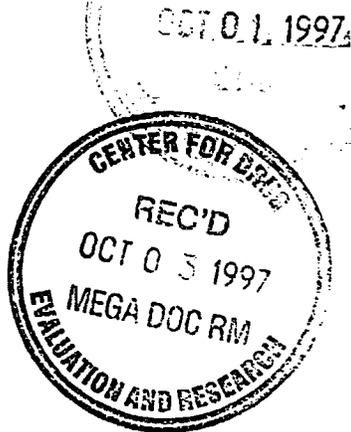
Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research



Pharmaceuticals

September 30, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833



Re: NDA 50-759
CellCept® Oral Suspension
(mycophenolate mofetil for oral suspension)

Dear Reviewers:

On behalf of Syntex (U.S.A.), Inc., and pursuant to section 505 of the Federal Food, Drug and Cosmetic Act, as amended, we are submitting a New Drug Application for CellCept® Oral Suspension (mycophenolate mofetil for oral suspension). This application pursues the approval of a novel oral suspension formulation of mycophenolate mofetil (MMF) as an alternative formulation to the approved oral forms of CellCept (capsules and tablets) for use in patients where the clinical condition causes difficulties to swallow solid oral dosage forms.

The oral suspension formulation is being investigated under IND for use in solid organ transplantation. CellCept Oral Suspension has been preassigned NDA number 50-759. (First NDA number 20-858 was preassigned, but following a request from Ms. Lisa Hubbard the number was changed to 50-759 on September 11, 1997.)

Mycophenolate mofetil is the subject of U.S. patent 4,753,935 and 4,786,637. This NDA contains information that constitutes Syntex's trade secret and commercial information; it is submitted, and exempt from public disclosure, under 21 CFR 20.61 (c).

The NDA was prepared in accordance with the regulations (21 CFR 314.50). The organization of the Sections is as follows:

<u>Section</u>	<u>Volumes</u>
I. Index to Application	1.1
II. Summary	1.2
III. Chemistry, Manufacturing and Controls	1.3 - 1.9
IV. Methods, Validation, Samples and Labeling	1.10 - 1.11

<u>Section</u>	<u>Volumes</u>
V. Nonclinical Pharmacology and Toxicology (not applicable)	---
VI. Human Pharmacokinetics and Bioavailability	1.12 - 1.19
VII. Microbiology (not applicable)	---
VIII. Clinical Data (not applicable)	---
IX. Safety Update (not applicable)	---
X. Statistical (not applicable)	---
XI. Case Report Form Tabulations (not applicable)	---
XII. Case Report Forms (not applicable)	---
XIII. Patent Information	See Volume 1.1

An overall table of contents for the application is included in Section I. In addition, a table of contents by section is included at the beginning of Section II - VI. A table of contents per each volume is also provided at the beginning of each volume. In order to assist the review of this NDA, the following documents are also provided:

- Reviewer's Guide: Located in Volume 1.1 and 1.2, this guide provides information on the format and content of each Section.
- Introductions to the Technical Sections: Located at the beginning of Sections III and VI, these introductions provide a brief description of the scope and format of those Sections.

In addition, electronic files (PDF/Acrobat and Microsoft Word Version 6.0) of all relevant CMC documents will be sent to the Division on October 20, 1997.

Electronic files (ASCII text files) containing the pharmacokinetic data from the studies included in Section VI are provided together with the reviewer's and archival copies.

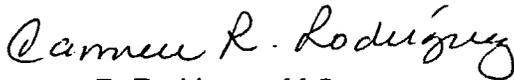
As agreed with the Division of Antiviral Drug Products in a February 7, 1997 teleconference, 6-month stability data of the three primary stability batches and 12-month data of the batch used in the bioequivalence study are included in this NDA. Roche will be submitting 12-month stability data of the three primary stability batches and 17-month data of the supportive batch by the end of February 1998.

We are submitting the archival copy of the NDA directly to the Central Document Room on Wilkins Avenue. The reviewer copies (chemistry, toxicology and biopharmaceutical) are being submitted directly to the Division of Special Pathogens and Immunological Drug Products. The field copies of Section III (Volumes 1.3 - 1.7) are being sent to the San Francisco District Office (applicant's home FDA district office) and to the New Jersey District Office (manufacturer's home FDA district office).

NDA 50-759
CellCept® Oral Suspension
September 30, 1997
page 3

Should you have any questions during the course of this review, please do not hesitate to contact either me by phone at (650) 354-2370 or fax (650) 852-1861 or Dr. Sabine Geisel at (650) 855-5923. We appreciate FDA's support in the development of the Mycophenolate Mofetil Program and look forward to continuing that cooperation during the review of this NDA.

Sincerely,



Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
Pharma Development Regulatory
Roche Global Development-Palo Alto, a Division of Syntex (U.S.A.) Inc.

Archival Copy:	Central Document Room
Reviewer Copies:	Division of Special Pathogens and Immunological Drug Products Center of Drug Evaluation and Research Food and Drug Administration 9201 Corporate Blvd. - 4th Floor Rockville, Maryland 20850
Vol. 1.1, 1.2, 1.9	Dr. Phillip Vincent, CDER
Vol. 1.3 - 1.9	San Francisco District Office (field copy) New Jersey District Office (field copy)
Vol. 1.1, 1.2	Ms. Lisa Hubbard (desk copy)

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: September 17, 1998
NDA: 50-759
PRODUCT: CellCept Suspension (mycophenolate mofetil for oral suspension)
APPLICANT: Syntex
BETWEEN: Dr. Sabine Geisel, 650-855-5923
and: Mark R. Seggel, Review Chemist, HFD-590 **157**

Background: In their September 9, 1998, amendment, Syntex referenced the two DMFs covering _____ and _____ Syntex also submit copies of Roche CoAs _____. On September 16, I left a voice message for Dr. Geisel, in which I indicated that I needed Letters of Authorization from the DMF holders, and the locations in the DMFs of the relevant information.

Discussion:

I called Dr. Geisel to follow-up on my previous voice-message. Dr. Geisel stated that the requested information was available and would be submitted to the NDA. The conversation was cordial throughout.

file: N50759mtc091798

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: August 28, 1998

NDA: 50-759

PRODUCT: CellCept Suspension (mycophenolate mofetil for oral suspension)

APPLICANT: Syntex

BETWEEN: Dr. Sabine Geisel, 650-855-5923

and: Mark R. Seggel, Review Chemist, HFD-590/S/

Discussion:

I initiated this call to Dr. Geisel to discuss several issues noted during my review of this original NDA application.

With regard to the manufacturer, to provide a Letter of Authorization to the relevant Drug Master File, if there was one, and to submit a representative manufacturer's Certificate of Analysis. In addition, I asked her to indicate in what aspects used in the drug product differed from Dr. Geisel thought that the vendor was reluctant to certify the product as because the product I then asked Dr. Geisel to provide the same type of information (manufacturer, LoA to DMF, representative manufacturer's CoA) for Dr. Geisel stated that she thought there was a DMF She will respond with more information on both

With regard to the regulatory specifications, I stated that they would need to add a test for to the drug product specifications. Dr. Geisel indicated that she would communicate this request to the CMC group at Syntex. I noted that I did not think the was sufficient to ensure product uniformity.

I then asked Dr. Geisel to confirm that stability studies on the commercial batches would be performed at the drug product manufacturing site in Nutley. Dr. Geisel stated that the commercial stability testing will be performed at Nutley.

Next, I asked Dr. Geisel to provide any information supporting the use of in the For example, reference to the CFR, USP/NF, or DMF would be helpful. She said that she would look into this.

I asked if . 110 g/225-cc) would be available for commercial distribution in the U.S. Dr. Geisel stated that at this time it was Syntex's intention to only market the 225-cc bottle in the U.S.

Lastly, I asked Dr. Geisel to confirm Syntex's plan to submit an updated stability report in September 1998 (18 mo. at 25°C/60% RH) to support 2 year expiration dating period. Dr. Geisel stated that the report should be available by September 8.

The conversation was cordial throughout.

APPEARS THIS WAY
ON ORIGINAL