

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50758

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

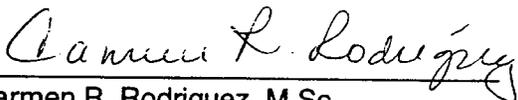
NDA 20-842

CellCept® Intravenous (mycophenolate mofetil hydrochloride injection)

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.

APPEARS THIS WAY
ON ORIGINAL



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

APPEARS THIS WAY
ON ORIGINAL

CellCept® Intravenous
(mycophenolate mofetil hydrochloride
injection) Powder for Solution



PATENT INFORMATION

PATENT INFORMATION

MYCOPHENOLATE MOFETIL is subject of U.S. patents 4,753,935 and 4,86,637.

MYCOPHENOLATE MOFETIL CRYSTALLINE ANHYDROUS SALTS (including hydrochloride) is subject of U.S. patent 5,543,408

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

CellCept® Intravenous (mycophenolate mofetil hydrochloride injection) Powder for Solution, 500 mg
NDA 20-842

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, drug product,
Patent No. 4,786,637; expires January 30, 2007;	method of use;
Patent No. 5,543,408; expires September 15, 2013;	drug, drug product.

The owner of the patents is:

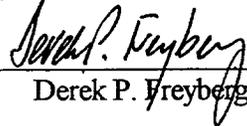
Syntex (U.S.A.) Inc.
3401 Hillview Avenue
Palo Alto, California 94304

APPEARS THIS WAY
ON ORIGINAL

DECLARATION

The undersigned declares that U.S. Patents Nos. 4,753,935; 4,786,637; and 5,543,408 cover the formulation, composition, and/or method of use of CellCept® Intravenous (mycophenolate mofetil hydrochloride injection) Powder for Solution, 500 mg. This product is the subject of this application for which approval is being sought.

APPEARS THIS WAY
ON ORIGINAL


Derek P. Freyberg

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 50-758 SUPPL # _____

Trade Name Cellep IV Generic Name mycophenolate mofetil hydrochloride injection
Applicant Name ROCHE HFD-590

Approval Date 8/11/98

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:

**APPEARS THIS WAY
ON ORIGINAL**

d) Did the applicant request exclusivity?

YES /___/ NO /~~X~~/

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).

APPEARS THIS WAY
ON ORIGINAL

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 # _____

APPEARS THIS WAY
ON ORIGINAL

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 # _____

APPEARS THIS WAY
ON ORIGINAL

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 / /

**APPEARS THIS WAY
ON ORIGINAL**

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:**

APPEARS THIS WAY
ON ORIGINAL

- (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: _____

APPEARS THIS WAY
ON ORIGINAL

- (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: _____

APPEARS THIS WAY
ON ORIGINAL

- (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 /___/

APPEARS THIS WAY
ON ORIGINAL

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 # _____

APPEARS THIS WAY
ON ORIGINAL

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 # _____

APPEARS THIS WAY
ON ORIGINAL

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: _____

APPEARS THIS WAY
ON ORIGINAL

- (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 _____

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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: _____

APPEARS THIS WAY
ON ORIGINAL

/S/

Signature

8/12/98
Date

Project Manager
Title

/S/

Signature of Division Director

Date

8/12/98

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)

NDA/PLA/PMA # **50-758** Supplement # Circle one: SE1 SE2 SE3 SE4 SE5 SE6
HFD-590

Trade and generic names/dosage form: CellCept® Intravenous (mycophenolate mofetil
hydrochloride injection)

Action: **AP** AE NA

Applicant Roche Global Development

Therapeutic Class 3S
Immunosuppressant

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 X inadequate ___

Indication 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.)

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.

APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

XX 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.**

APPEARS THIS WAY
ON ORIGINAL

/S/

APPEARS THIS WAY
ON ORIGINAL

Signature of Preparer and Title:

Mary Dempsey, Project Manager Date: August 12, 1998

cc: Orig NDA/PLA/PMA # 50-758

HFD-590 /Div File

NDA/PLA Action Package

HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

APPEARS THIS WAY
ON ORIGINAL

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. (revised)

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: February 19, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex
BETWEEN: Ms. Carmen Rodriquez, 650-354-2370
and: Mark R. Seggel, Review Chemist, HFD-590 /S/

Discussion:

APPEARS THIS WAY
ON ORIGINAL

I called Ms. Rodriquez to discuss t
Ms. Rodriquez said

I then asked if the hydrochloride salt of MMF had been assigned a CAS number and a USAN name. She agreed to check on this question as well.

APPEARS THIS WAY
ON ORIGINAL

The conversation was cordial throughout.

file: N50758mtc021998

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: May 8, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex
BETWEEN: Dr. Sabine Geisel, 650-855-5923
and: Mark R. Seggel, Review Chemist, HFD-590

APPEARS THIS WAY
ON ORIGINAL

/S/

Background: This telephone conversation was initiated by the reviewer to request (1) additional information, (2) revision of the stability protocol, and (3) revision of the drug product specifications.

Discussion: I began by explaining that

noted that the three registration batches

I also noted
I requested

Next, I stated that the stability protocol should be revised to include
will be performed at release and at
the expiry. [Syntex had proposed only stability testing at release and at the expiry.]

Finally, I asked Dr. Geisel
report were prepared and stored. She speculated
She agreed to provide more detailed information.

Dr. Geisel stated that she would need to discuss these issues with the Syntex CMC group before she could respond.

The conversation was cordial throughout.

file: N50758mtc050898

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: May 12, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex
BETWEEN: Dr. Sabine Geisel, 650-855-5923
and: Mark R. Seggel, Review Chemist, HFD-590

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/s/

Background: This telephone conversation was initiated by the applicant to follow up on the issues discussed on May 8, 1998.

APPEARS THIS WAY
ON ORIGINAL

Discussion: Dr. Geisel asked for clarification
I explained

Sterility testing should be conducted at release and at the expiry. The need when additional experience with the product had been gained.

APPEARS THIS WAY
ON ORIGINAL

Dr. Geisel stating that Syntex would like

The conversation was cordial throughout.

file: N50758mtc051298

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: May 13, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex (Roche)
BETWEEN: Dr. Sabine Geisel, Roche
Ms. Alice Varga, Roche
Ms. Deborah Lidgate, OREAD
Ms. Mary Ann Lee, OREAD
and: Mark R. Seggel, Review Chemist, HFD-590 /S/

APPEARS THIS WAY
ON ORIGINAL

Background: This telephone conversation was initiated by the applicant in order to discuss our request (telephone conversation on May 8)

Discussion: Syntex has proposed the following limits for mycophenolic acid (MPA) in the drug product

APPEARS THIS WAY
ON ORIGINAL
Syntex

These limits are not supported by the agreed

The limit is derived from the following:

APPEARS THIS WAY
ON ORIGINAL

However, the

samples exceeding

The only

The conversation was cordial throughout.

APPEARS THIS WAY
ON ORIGINAL

file: N50758mtc051398

Note: Dr. Schmuff and I have discussed this at length, and believe

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: May 19, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex
BETWEEN: Dr. Sabine Geisel, 650-855-5923
and: Mark R. Seggel, Review Chemist, HFD-590 /S/

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Background: I called Dr. Geisel to follow up on our previous discussions regarding setting the specification for MPA in the IV product.

APPEARS THIS WAY
ON ORIGINAL

Discussion: I explained to Dr. Geisel that I had consulted with both my Team Leader and our Supervisor in the IV drug product. I stated that they agreed

APPEARS THIS WAY
ON ORIGINAL

Dr. Geisel expressed her concern

Syntex' rationale would again have to consult with the CMC group regarding this issue.

She reiterated
Dr. Geisel indicated that she

The conversation was cordial throughout.

file: N50758mtc051998

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION--HFD-590

DATE: June 16, 1998
NDA: 50-758
PRODUCT: CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
APPLICANT: Syntex
BETWEEN: Dr. Sabine Geisel, 650-855-5923
and: Mark R. Seggel, Review Chemist, HFD-590

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

/S/

Notes:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

This telephone call to Dr. Geisel was initiated to discuss several issues related to the chemistry, manufacturing and controls for CellCept Intravenous. Reference was made to the applicant's May 22, 1998, response to our request (see Memorandum of telephone Conversation, May 8, 1998)

I inquired as to whether Syntex

Dr. Geisel confirmed that they I then asked when we would receive the revised drug product specifications. Dr. Geisel stated that they would be submitted sometime this week. I then asked Dr. Geisel to confirm that had requested samples for She stated that

The conversation was cordial throughout.

file: N50758mtc061698

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-758

APPEARS THIS WAY
ON ORIGINAL

•Roche Global Development
3403 Hillview Avenue
Palo Alto, CA 934-1987
Attention: Ms. Carmen Rodriquez, Program Director
Drug Regulatory Affairs

JAN 7 1998

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Rodriquez:

Please refer to your Investigational New Drug Application (NDA) submitted pursuant to section 505 of the Federal Food, Drug and Cosmetic Act for CellCept® (mycophenolate mofetil hydrochloride injection).

APPEARS THIS WAY
ON ORIGINAL

Reference is also made to your letter of December 8, 1997, requesting a waiver of the requirements for the submission of a 4-month safety update for NDA 50-758 in conjunction with your New Drug Application (NDA) for CellCept® (mycophenolate mofetil hydrochloride injection).

APPEARS THIS WAY
ON ORIGINAL

We have concluded that your request for a waiver of the requirements for the submission of a 4-month safety update for NDA 50-758 is acceptable.

APPEARS THIS WAY
ON ORIGINAL

Should you have any further questions concerning this NDA, please contact Mary Dempsey, Project Manager, at 301-827-2335.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

/s/

APPEARS THIS WAY
ON ORIGINAL

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

~~ORIG AMENDMENT~~



ORIGINAL

Pharmaceuticals

June 16, 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



Re: NDA 50-758
CellCept® Intravenous
(mycophenolate mofetil hydrochloride for injection)
Response to CMC Questions Received by Phone on May 8, 1998
Here: Submission of Revised Specifications (as addressed in our letter of May 22, 1998)

Dear Reviewers:

Please find attached the revised specifications and directions for testing for the finished product CellCept Intravenous as addressed in our letter of May 22, 1998.

In the letter of May 22, 1998 we responded to three CMC questions which we received on May 8, 1998 by phone.

The herein submitted specifications have been changed as follows:

We thank you for your continued support of the CellCept program. Please do not hesitate to contact either Mrs. Carmen Rodriguez at (650) 354-2370 or me at (650) 855-5923 should you require additional information.

Sincerely,

Dr. Sabine Geisel
Regulatory Program Manager

Att. Ms. Mary Dempsey
via: Federal Express

Phone: (415) 855-5050

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

3401 Hillview Avenue
Palo Alto
California 94304-1397

June 16, 1998

NC
ORIGINAL



Pharmaceuticals

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

APPEARS THIS WAY
ON ORIGINAL



RE: NDA 50-758
CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)
Proposal for Final Labeling; Request for a Telecon

Dear Reviewers:

APPEARS THIS WAY
ON ORIGINAL

We have received your letter of June 15, 1998 with the proposed revisions to the label for CellCept Intravenous.

Proposed attendees from Roche, Palo Alto will be Dr. Andrew Nicholls, Clinical Pharmacologist, and Ms Carmen Rodriguez and Ms Alice Varga, Regulatory Affairs.

Please call me directly at (650) 354-7477 to further discuss the timing of this telecon. I can also be reached by fax at (650) 855-5589. Ms Rodriguez can be reached by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Alice M. Varga, M.A.
Regulatory Affairs Associate

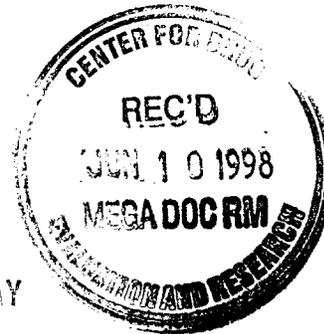
Copies via FedEx: (2), Desk Copy (1) for Ms Mary Dempsey
Desk Copy (1) for Ms Mary Dempsey, via Fax



Pharmaceuticals

June 8, 1998

APPEARS THIS WAY
ON ORIGINAL



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

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: NDA 50-758, CellCept® Intravenous (mycophenolate mofetil hydrochloride)
Resubmission of Letter for Name Change for Manufacturer

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers:

As per the request of Ms Mary Dempsey, CSO by voice mail on June 8, 1998

Thank you for your continuing assistance for the New Drug Application for CellCept® Intravenous. Should you have any questions, please feel free to contact me by phone at (650) 354-7477 or by facsimile at (650) 852-1861 or Carmen R. Rodriguez by phone at (650) 354-2370 or by facsimile at (650) 852-1861.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Alice M. Varga

Alice M. Varga, M.A.
Regulatory Associate

FDA (2)
Desk Copy: Ms. Mary Dempsey, CSO
FAX: Ms. Mary Dempsey, CSO

DESK COPY FOR
/S/
OFFICIAL COPIES
HAVE BEEN SUBMITTED
TO APPROPRIATE IND
OR NDA

APPEARS THIS WAY
ON ORIGINAL



Pharmaceuticals

April 15, 1998

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

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: NDA 50-758, CellCept® Intravenous (mycophenolate mofetil hydrochloride)
Name Change for Manufacturer

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers:

This is to inform you that the name of the site for the manufacture, packaging and quality control release for CellCept® Intravenous (mycophenolate mofetil hydrochloride) has been changed from:

Parke-Davis
870 Parkdale Road
Rochester, MI 48307

APPEARS THIS WAY
ON ORIGINAL

to:

Parkedale Pharmaceuticals, Inc.
870 Parkdale Road
Rochester, MI 48307

Thank you for your continuing assistance for the New Drug Application for CellCept® Intravenous. Should you have any questions, please feel free to contact me by phone at (650) 354-7477 or by facsimile at (650) 852-1861 or Carmen R. Rodriguez by phone at (650) 354-2370 or by facsimile at (650) 852-1861.

Sincerely,

Alice M. Varga, M.A.
Regulatory Associate

APPEARS THIS WAY
ON ORIGINAL

FDA (2)
Desk Copy: Ms. Mary Dempsey, CSO
FAX: Ms. Mary Dempsey, CSO

NC
ORIGINAL



Pharmaceuticals

May 29, 1998

Ms. Mary Dempsey, CSO
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 4th Floor
Rockville, MD 20850



APPEARS THIS WAY
ON ORIGINAL

Re: NDA 50-758 - CellCept® Intravenous
(mycophenolate mofetil hydrochloride for injection)

APPEARS THIS WAY
ON ORIGINAL

Dear Ms. Dempsey,

I am attaching a copy of a letter dated May 12, 1998 which we just received
Mr. Israel Santiago of the Office of Regulatory Affairs, HFC-170. The
letter

The remaining points were
addressed in an earlier letter to Mr. Santiago dated March 10, 1998.

We believe that the May 12, 1998 letter to Mr. Santiago completes
and ask for your confirmation of this fact.

Thank you for your continuing assistance in the development program for
mycophenolate mofetil. Should you have any questions, please contact me by phone at
(650) 354-7477 or by fax at (650) 852-1861.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

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

ORIGINAL



NEW CORRESP

CC

Pharmaceuticals

May 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

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 50-758
CellCept® Intravenous
(mycophenolate mofetil hydrochloride for injection) 500 mg

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers:

Intravenous.

on NDA 50-758 for CellCept
APPEARS THIS WAY
ON ORIGINAL

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

Sincerely,

Dr. Sabine Geisel
Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL



Att.: Ms. Mary Dempsey
via: facsimile

ORIGINAL



Pharmaceuticals

APPEARS THIS WAY
ON ORIGINAL

bc



February 20, 1998

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

APPEARS THIS WAY
ON ORIGINAL

Re: NDA 50-758, CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)
Response to questions from Dr. Mark Seggel

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers,

This letter is in response to the comments and the request for clarification made by Dr. Mark Seggel in a teleconference with Ms Carmen Rodriguez on February 19, 1998.

Following are our responses to Dr. Seggel's comments.

There is no USAN name nor a CAS number for CellCept® Intravenous (mycophenolate mofetil hydrochloride).

The CAS number for this compound is 128794-94-5. We are presently applying for a USAN name and will notify FDA when we receive approval for it.

Please contact me by phone (650-354-7477) or fax (650-852-1861) or Ms Carmen Rodriguez at 650-354-2370 (phone), 1-800-943-8587 (pager), or 650-852-1861 (fax) if there are any questions.

Sincerely,

Alice M. Varga

Ms Alice M. Varga, MA
Regulatory Associate, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

Desk Copies (3) for Ms Lisa Hubbard
Via: fax and courier

APPEARS THIS WAY
ON ORIGINAL

~~HE~~ BI
NEW CORRESP
ORIGINAL



Pharmaceuticals

February 10, 1998.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogens and Immunologic Drug Products, HFD-590
9201 Corporate Blvd.
Rockville, MD 20850



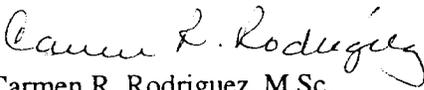
Subject:
CellCept® Intravenous (mycophenolate mofetil hydrochloride injection) - NDA 50-758
Responses to Microbiology Questions Received on February 5, 1998.

APPEARS THIS WAY

Dear Reviewers:
Attached please find our response to the two microbiology questions on NDA 50-758 for CellCept Intravenous

We greatly appreciate the Division's cooperation in assisting Roche to pursue the approval of the NDA for the intravenous formulation for CellCept. Should you have any questions please do not hesitate to contact me by phone [650 354-2370], pager [1-800-943-8587] or fax [650 852-1861].

Sincerely,


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

APPEARS THIS WAY
ON ORIGINAL

Att: Ms. Mary Dempsy
via: facsimile

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL



BB
ORIG AMENDMENT

Pharmaceuticals

January 30, 1998

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



SUBJECT: NDA 50-758 - CellCept® Intravenous
(mycophenolate mofetil hydrochloride injection)
Submission of 36 month stability data

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers:

We are hereby submitting

This addendum provides 36-month stability data for the registration lots (Lots 61443-000-902051, 60443-000-902061 and 61443-000-987021) and up to 12-month stability data for an additional lot (Lot 61443-000-1516371).

Thank you for your continuing assistance in the development program for mycophenolate mofetil. Should you have any questions, please contact me at by phone at (650) 354-2370 or by facsimile at (650) 852-1861.

Sincerely,

Alia M. Yarga

Carmen R. Rodriguez, M. Sc. *for*
Sr. Regulatory Program Manager

APPEARS THIS WAY
ON ORIGINAL

Desk Copies (3) Ms Mary Dempsey

APPEARS THIS WAY
ON ORIGINAL



Pharmaceuticals

ORIGINAL

ORIG AMEND

BC

January 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 20850



APPEARS THIS WAY
ON ORIGINAL

Re: Environmental Assessment Report - Application for Categorical Exclusion for
NDA 50-758 CellCept Intravenous

APPEARS THIS WAY
ON ORIGINAL

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 50-758. 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.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Carmen R. Rodriguez

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

APPEARS THIS WAY
ON ORIGINAL

cc: Dr. Mark Seggel

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

ORIGINAL



Pharmaceuticals

December 8, 1997

APPEARS THIS WAY

SU



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogens and Immunologic Drug Products, HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

Re: CellCept® Intravenous (mycophenolate mofetil hydrochloride injection), NDA 50-758
Request for a letter of agreement for an exemption to the requirement for the submission of the 4-month safety update to NDA 50-758

We refer to the Roche request for an agreement from the Division for an exemption from the requirement for a 4-month safety update for NDA 50-758 for CellCept® Intravenous discussed with Ms Mary Dempsey and Ms Lisa Hubbard (October 30, and November 14, respectively).

During the teleconference with Ms Lisa Hubbard on November 14, 1997, it was stated that the medical reviewer for the intravenous NDA had agreed to the requested exemption for the above mentioned reasons. As agreed with Ms Lisa Hubbard during this teleconference, Roche would like to request a letter of agreement for an exemption to the requirement for the 4-month safety update for NDA 50-758 for CellCept® Intravenous, due on December 29, 1997.

Please contact me by phone [650-354-2370], pager [1-800-943-8587] or fax [650-852-1861] if there are any questions.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Carmen R. Rodriguez

Ms Carmen R. Rodriguez, MS
Program Director, Drug Regulatory Affairs

NAI -
1-30-98
/S/

Desk Copies (3) for Ms Lisa Hubbard
Via: fax and courier

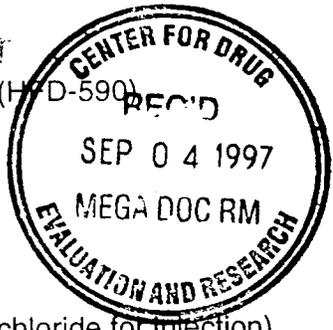


Pharmaceuticals

September 2, 1997

ORIG AMENDMENT

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 20850



Subject: NDA 20-842
CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)
Powder for Solution 500 mg
Pharmacokinetic Datasets on Diskette

APPEARS THIS WAY
ON ORIGINAL

Dear Reviewers:

As committed in the cover letter for NDA 20-842, CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection) Powder for Solution 500 mg, enclosed please find a diskette containing the pharmacokinetic data from mycophenolate mofetil studies MYCs 030, MYC 061, MYCx 1900, MYCc 2104, MYCc 2118, MYCi 2176, MYC 2294, MYCS 2378 and MYCS 2734. This diskette is provided to facilitate the review of application submitted to the agency on August 29, 1997.

APPEARS THIS WAY
ON ORIGINAL

In addition, documents for Data Release Approval and Diskette Directory/File Structure are attached. As noted, all data files are in tab-delimited ASCII format. The ".DAT" files contain concentration-time data, the ".PKV" file contain computed pharmacokinetic parameters, the ".DMH" files contain demographic information and the ".AER" files contain pharmacokinetic data collected following rejection or certain adverse events. Also, note that 1) actual sampling times (not nominal) were used to calculate all pharmacokinetic variables and 2) for all MPAG files, while raw concentrations are given in the ".DAT" files, the ".PKV" files contain the variables calculated using MPA equivalent units. All data are accurate and complete to the best of our knowledge.

APPEARS THIS WAY
ON ORIGINAL

We appreciate your continuous support to the mycophenolate mofetil development program. Please feel free to contact me at (415) 852-1827 if you have any questions.

Sincerely,

Irfan Mahmood, MBBS
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Enclosures: Archival copy (with diskette)
Reviewer's copy (with diskette)
Desk copy for Ms. Lisa Hubbard (with diskette)



August 29, 1997

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

APPEARS THIS WAY
ON ORIGINAL

SUBJECT: NDA 20-842
CellCept® Intravenous (mycophenolate mofetil hydrochloride injection)
Powder for Solution 500 mg.

Dear Reviewers:

APPEARS THIS WAY
ON ORIGINAL

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® Intravenous (mycophenolate mofetil hydrochloride injection). This application pursues the approval of a novel intravenous formulation of mycophenolate mofetil (MMF) as an alternative dose form to the approved oral forms of CellCept (capsules and tablets) for use in patients unable to tolerate oral dosage forms.

APPEARS THIS WAY
ON ORIGINAL

CellCept Intravenous has been preassigned NDA number 20-842. The intravenous formulation of

Mycophenolate mofetil is the subject of U.S. patents 4,753,935 and 4,786,637. Mycophenolate mofetil hydrochloride is subject to U.S. patent 5,543,408. 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).

APPEARS THIS WAY
ON ORIGINAL

As agreed with the Division of Antiviral Drug Products in a June 20, 1996 teleconference, this application is supported, primarily, by comparative pharmacokinetics data of the oral and IV dose forms of mycophenolate mofetil, and an account of the safety experience obtained for the intravenous dose form with an emphasis on data from a controlled study comparing safety of the two dose forms.

This NDA was prepared in accordance with the regulations (21 CFR 314.50). The format of the NDA was reviewed and agreed upon during a teleconference (March 14, 1997) between representatives of Roche Global Development and the Division of Antiviral Drug Products. The organization of the Sections is as follows:

<u>Section</u>	<u>Volumes</u>
I. Index to Application	1.1
II. Summary	1.2-1.3

APPEARS THIS WAY
ON ORIGINAL

K:\V\FILING\LTR_FDA\NDA-IVC2.DOC.1

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

3401 Hillview Avenue
Palo Alto
California 94304-1397

Phone: (415) 855-5050

MEMORANDUM OF TELEPHONE MEETING WITH INDUSTRY

DATE: August 7, 1998

NDA: 50-758

APPEARS THIS WAY
ON ORIGINAL

DRUG: CellCept IV

APPLICANT: Roche Global Development

FDA ATTENDEES: Marc Cavaille'-Coll, M.D, Ph.D, Team Leader
Joyce Korvick, M.D., Medical Officer
Kofi Kumi, Ph.D., Biopharmaceutics
Rene Kimzey, Project Manager
Mary Dempsey, Project Manager

APPEARS THIS WAY
ON ORIGINAL

ROCHE ATTENDEES: Dr. Eleanor Ramos
Dr. Andrew Nicholls
Dr. Debra Vallner
Ms. Deborah Lidgate
Ms. Maryann Lee
Dr. Sabine Geisel

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The purpose of this teleconference was to negotiate the proposed CellCept IV label. Roche received the labeling fax the Agency sent on August 5, 1998.

Roche response to our labeling comments is as follows:

Biopharm labeling comment:
acceptable

APPEARS THIS WAY
ON ORIGINAL

Clinical labeling comments:

- line 603: will be revised to "...immediate transplant period (administered for first 5 days post transplant)."



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE Food and Drug Administration
Rockville MD 20857

DATE: August 5, 1998

TO: Sabine Geisel, Regulatory Affairs
Roche Global Development

FROM: Mary Dempsey, Project Manager

THROUGH: Joyce Korvick, M.D.
Kofi Kumi, Ph.D., Biopharmaceutics

NDA: 50-758

DRUG: CellCept IV

SUBJECT: Label revisions

APPEARS THIS WAY
ON ORIGINAL

Biopharm Additional Labeling Comments:

Please delete lines 196 to 198. The statement is not necessary. It provides a suggestion that the 23 mg/kg dose is optimal for the pediatric patients but there is not sufficient information to accurately determine the optimum dose.

APPEARS THIS WAY
ON ORIGINAL

Clinical labeling comments:

Line 603: "...immediate posttransplant period" ADD (administered for the first 10-11 doses/ 5-6 days).

Line 652/653: It think this should be move up to the end of the first paragraph and make caps of NO LESS THAN 2 HOURS.

APPEARS THIS WAY
ON ORIGINAL

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Mary Dempsey /S/ U
Project Manager
Division of Special Pathogens and Immunologic Drug Products

APPEARS THIS WAY
ON ORIGINAL