

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

CHEMISTRY REVIEW(S)

**DIVISION OF SPECIAL PATHOGEN AND
IMMUNOLOGIC DRUG PRODUCTS—HFD-590**
Review of Chemistry, Manufacturing and Controls Section

NDA #: 21-083

CHEMISTRY REVIEW #: 1

REVIEW COMPLETED: August 30, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	December 15, 1998	December 15, 1999	December 21, 1999
NC	January 6, 1999	January 6, 1999	January 13, 1999
BC (container/closures)	February 17, 1999	February 18, 1999	March 2, 1999
NC	March 22, 1999	March 23, 1999	March 30, 1999
BC	March 23, 1999	March 24, 1999	March 30, 1999
BC	March 29, 1999	March 30, 1999	April 8, 1999
BC (dp stability update)	April 26, 1999	April 27, 1999	-
BC (response to info req.)	April 29, 1999	May 3, 1999	May 19, 1999
BC (ds stability update)	May 26, 1999	May 27, 1999	June 10, 1999
BL (containers/cartons)	August 5, 1999	August 9, 1999	August 11, 1999
BC (response to info req.)	August 17, 1999	August 18, 1999	August 20, 1999
BC (response to info req.)	August 19, 1999	August 20, 1999	August 24, 1999
BC	August 24, 1999	August 25, 1999	August 26, 1999
BL	August 25, 1999	August 25, 1999	-

NAME/ADDRESS OF APPLICANT: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAME:

Proprietary: Rapamune Oral Solution
Nonproprietary: sirolimus oral solution
Other: rapamycin
Code Name: AY-22989; WY-090217

CHEM. TYPE/THER. CLASS:

1P

DRUG CLASS:

5010400

PHARMACOLOGICAL CATEGORY:

Immunosuppressant

INDICATION:

The prophylaxis of organ rejection in patients receiving renal transplants

DOSAGE FORM/STRENGTH:

Oral solution, 1 mg/mL

ROUTE OF ADMINISTRATION:

Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentacontine-1,5,11,28,29(4H,6H,31H)-pentone

definition of an antibiotic. With the elimination of the regulations pertaining to antibiotics, rapamycin is now handled as other drug products and is numbered accordingly.

RELATED DOCUMENTS:

DMF

IND

CONSULT REVIEWS:

Trade Name (Reviewed by CDER Labeling and Nomenclature Committee)

REMARKS/COMMENTS:

Sirolimus, also known as rapamycin, is a macrocyclic lactone antibiotic produced by *Streptomyces hygroscopicus*, an actinomycete first isolated in 1975 from a soil sample collected on Rapa Nui, more commonly known as Easter Island. Rapamycin is structurally related to the immunosuppressant tacrolimus (FK-506; Prograf) and was originally isolated in a discovery program for antifungal agents.

DRUG SUBSTANCE

2 pages

Redacted

TRADE SECRET/

Confidential

Commercial

ESTABLISHMENT EVALUATION

As of June 2, 1999, the drug substance and drug product manufacturing and testing facilities had acceptable cGMP status (see attached EES report). While some questions were raised during the inspection of the [redacted] facility, no FDA Form 483 was issued. The questions appear to have been adequately addressed by the manufacturer.

METHODS VALIDATION

The analytical methods for the control of the drug substance and drug product appear to be suitable for the intend uses. The submitted validation data appears to be adequate. Two FDA laboratories [redacted] have been asked to confirm the suitability of the methods. FDA lab work is not completed at this time. The NDA Action Letter should include a request for the continued cooperation of the applicant should any questions arise or if modifications to the methods are deemed necessary.

LABELING

The CDER Labeling and Nomenclature Committee has found the proprietary name, Rapamune, acceptable. The Title, Description and How Supplied sections of the package insert as presented in BL 8/25/99 are acceptable. Minor changes to those sections of the package insert have been made. The storage statement has been revised. The container, pouch and carton labels are acceptable as presented in BL 8/5/99. Changes to the appearance of the proprietary name and placement of the generic name were made on all labels. A statement of the percentage of alcohol in the product was added to the labels as required under by Section 502(e)(1) of the FD&C Act.

ENVIRONMENTAL ASSESSMENT

The Expected Introduction Concentration (EIC) is [redacted]. A categorical exclusion from the environmental assessment requirements is claimed in accordance with the revised regulations published in the July 29, 1997, Federal Register (21 CFR 25.31(b)). The applicant knows of no extraordinary circumstances associated with the proposed action. The categorical exclusion is acceptable.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

4.4 Environmental Assessment

August 3, 1998

Environmental Assessment

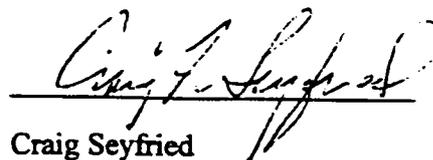
Statement of Compliance

The Expected Introduction Concentration (EIC) of Rapamune® (sirolimus), is [redacted]

Wyeth-Ayerst Pharmaceuticals states that an Environmental Assessment (EA) for the proposed action, the New Drug Application for Rapamune® (sirolimus), Oral Liquid, [redacted] is excluded according to revisions to the policies and procedures of the National Environmental Policy Act (NEPA) of 1969 as announced in the July 29, 1997 Federal Register notice.

Page 40595 of the FR announcement of the Final Rule discusses 21 CFR 25.31(b) which covers human drugs and biologics. The aforementioned regulation states that a categorical exclusion is permitted for "Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be _____"

To the best knowledge of Wyeth-Ayerst Pharmaceuticals, no extraordinary circumstances exist associated with the proposed action.



Craig Seyfried
Senior Director
Environmental, Health & Safety
Wyeth-Ayerst Pharmaceuticals