Roche

January 30, 2002

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Dr. Jonathan Wilkin
Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard, 2nd Floor
Rockville, Maryland 20850

Dear Dr. Wilkin:

Re: **NDA 18-662 – Accutane (isotretinoin) Capsules**
Information Request: Response to FDA Fax of November 26, 2001

Reference is made to the FDA fax of November 26, 2001 in which FDA requested that Roche submit all pre-clinical data and/or study reports from any Hoffmann-La Roche facility or location from any year pertaining to the effects of isotretinoin on behavior or central nervous system function.

Roche has reviewed all pre-clinical data and/or study reports available and has contacted key Roche affiliates concerning this matter. In this process, we have found an internal research report entitled "General pharmacological and drug interaction studies with Ro 04-3780 (13-cis retinoic acid) administered orally." We are hereby submitting this report.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Joanna Waugh, BSc., Hons.
Group Director
Drug Regulatory Affairs
(973) 562-2566 (phone)
(973) 562-3700 (fax)

JW/gb

HLR NO. 2002-295
Attachment

Desk copies: Mary Jean Kozma-Fornaro, HFD-540 (2)
Dr. Kathryn O'Connell, HFD-540

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

HLR 111313

NDA 18-662
Accutane (isotretinoin) Capsules

Information Request: Response to FDA Fax of November 26, 2001

Hoffmann-La Roche Inc. January 30, 2002

ACCUTANE

Response to FDA FAX of 11/26/2001

NDA #:18-662 VOL#: 1 of 1
SER#: RO#: 4-3780
01/31/2002 314067

HLR 111310

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoffmann-La Roche Inc	January 31, 2002
TELEPHONE NO. *(Include Area Code)* (973) 562-2566	**FACSIMILE (FAX) Number** *(Include Area Code)* (973) 562-3700/3554
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)* 340 Kingsland Street Nutley, N.J. 07110	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Joanna Waugh, BSc., Hons Group Director Drug Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 18-662

ESTABLISHED NAME *(e.g. Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Isotretinoin	Accutane

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: 13 cis-retinoic acid

CODE NAME *(If any)*: Ro 04-3780

DOSAGE FORM:	STRENGTHS	ROUTE OF ADMINISTRATION:
Capsules	10 mg, 20 mg, and 40 mg	Oral

(PROPOSED) INDICATION(S) FOR USE

Severe Recalcitrant Nodular Acne

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*

☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☑ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Information Request: Response to FDA Fax of November 26, 2001

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

NUMBER OF VOLUMES SUBMITTED: _____ THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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

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

HLR 111311

This application contains the following items: *(Check all that apply)*	
	1 Index
	2 Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3 Summary (21 CFR 314.50(c))
	4 Chemistry section
	A Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
	C Methods validation package (e.g., 21 CFR 314.50(e)(2)(i), 21 CFR 601.2)
	5 Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6 Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3), 21 CFR 601.2)
	7 Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8 Clinical data section (e.g., 21 CFR 314.50(d)(5), 21 CFR 601.2)
	9 Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
	10 Statistical section (e.g., 21 CFR 314.50(d)(6), 21 CFR 601.2)
	11 Case report tabulations (e.g., 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12 Case report forms (e.g., 21 CFR 314.50 (f)(2), 21 CFR 601.2)
	13 Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14 A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15 Establishment description (21 CFR Part 600, if applicable)
	16 Debarment certification (FD&C Act 306 (k)(1))
	17 Field copy certification (21 CFR 314.50 (k)(3))
	18 User Fee Cover Sheet (Form FDA 3397)
	19 Financial Information (21 CFR Part 54)
✔	20 OTHER *(Specify)* Information Request: Response to FDA Fax of November 26, 2001

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations. Parts 606, and/or 820
2. Biological establishment standards in 21 CFR Part 600
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Joanna W	Joanna Waugh, BSc., Hons, Group Director, DRA	January 31, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
348 Kingsland Street, Nutley New Jersey 07110	(973) 562-2566

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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FORM FDA 356h (4/00)