DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-662/S-056

Hoffman La-Roche
Attention: Ellen Carey, Senior Program Manager
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms Carey:

Please refer to your pending supplemental new drug application submitted June 24, 2005, received June 27, 2005 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accutane (isotretinoin) Capsules, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated July 1, July 14, July 21, July 26, July 28, July 29, August 2, August 3, August 5, August 9, and August 11, 2005.

This supplemental application, considered for approval under 21 CFR 314.520 (Subpart H), at your request because of the teratogenicity of isotretinoin, proposes the iPLEDGE program, an enhanced risk minimization action plan (RiskMAP) designed to minimize drug exposure during pregnancy.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to approve the supplemental application for Accutane (isotretinoin) Capsules, 10mg, 20mg, and 40mg. You have indicated your agreement with approval under 21 CFR 314.520 (Subpart H). Accordingly, this supplemental application is approved under 21CFR 314.520 (Subpart H). Approval is effective on the date of this letter for use as recommended in the agreed upon labeling and the components of the iPLEDGE RiskMAP.

Accutane RiskMAP

We remind you that your Accutane RiskMAP (called iPLEDGE) is an important part of the postmarketing risk management for Accutane, and must include each of the following components:

1. Registration in the iPLEDGE program of wholesalers, prescribers, pharmacies, and patients who agree to accept specific responsibilities in order to distribute, prescribe, dispense, and use Accutane.
2. Implementation of a program and distribution of materials to educate wholesalers, prescribers, pharmacists, and patients about the risks and benefits of Accutane.
3. Implementation of a reporting and data collection system for: 1) serious adverse events associated with the use of Accutane that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) and 2) sales and dispensing of Accutane outside of the iPLEDGE program.
4. Implementation of a plan to monitor, evaluate, and improve minimization of drug exposure during pregnancy and compliance with restrictions for safe use under the iPLEDGE program.

A component of the evaluation program includes a pregnancy registry to elucidate the root cause of potential RiskMAP failure.

The iPLEDGE program, as described in the attached documents, adequately addresses each of these requirements. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA's determination that the required components continue to be met. We expect your continued cooperation to resolve any problems regarding the iPLEDGE program that may be identified following approval of this supplement.

We remind you of your specific reporting obligations regarding serious adverse events in patients who have received Accutane. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), you will submit a 15-day report for each of the following:

- All pregnancy exposures to Accutane; and
- All psychiatric events including suicides, attempted suicides, and suicidal ideation

Within the first year of initiation of the iPLEDGE program, and at the specified time frames thereafter, in addition to the Periodic Adverse Drug Experience Report required under 21 CFR 314.80(c), you must provide FDA with the following reports that will evaluate the success of the program in achieving program goals and compliance with program restrictions and requirements.

1. Special Pregnancy Periodic Quarterly Report: A quarterly report that provides information on U.S. maternal and fetal exposures to Accutane.
2. iPLEDGE Program Evaluation Report: A quarterly report that includes evaluation of program components and the rate of compliance with each in accordance with the Process Compliance Evaluation Plan discussed below, including sponsor adherence to restrictions of drug distribution to registered wholesalers, oversight of wholesaler, prescriber, pharmacy and patient compliance with relevant program requirements, and oversight of the iPLEDGE data base.
3. Non-Compliant Distribution Reports: Special reports submitted to the Division of Compliance Risk Management and Surveillance for each known occurrence during the interval since the last Program Evaluation report of: a) sale of any Accutane product by a wholesaler to an unregistered and/or un-activated pharmacy or unregistered wholesaler, b) dispensing of any Accutane product by an unregistered and/or un-activated pharmacy, and c) corrective action taken by Hoffman La-Roche for each occurrence under a) and b). These reports will be submitted within 15 days of the sponsor's receipt of new information to the following address:

   Division of Compliance Risk Management and Surveillance (HFD-330)
   Office of Compliance
   Center for Drug Evaluation and Research
   Food and Drug Administration
   5600 Fishers Lane
   Rockville, MD 20857

The content of the reports, objectives and plans for evaluation, and correction of noncompliant behavior are further described in the attached "Accutane Risk Minimization Action Plan: Summary of iPLEDGE".

To further assist FDA in evaluating any reported adverse events associated with the use of Accutane and to assist FDA in evaluating the success of the iPLEDGE program in preventing exposure of the drug in pregnant women, the Annual Periodic Adverse Drug Experience Report [required under 314.80(c)(2)], the Psychiatric Quarterly Report, the Special Pregnancy Report, and the iPLEDGE Program Evaluation Report will be submitted on the harmonized schedule below. The harmonized time frames are based on the date of mandatory compliance with the iPLEDGE program, December 31, 2005. It is understood that the initial reports may not represent a full calendar quarter or year, as appropriate. The following chart provides the harmonized specific quarterly and annual time periods for these reports:

	Reporting Period: Quarterly Reports
Quarter 1	January 1 – March 31 *(the first report for 2006 will cover December 31, 2005 – March 31, 2006)*
Quarter 2	April 1 – June 30
Quarter 3	July 1 – September 30
Quarter 4	October 1 – December 31
	Reporting Period: Annual Reports
	January 1 – December 31 *(the first report will cover December 31, 2005 through December 31, 2006)*

In addition, a "close-out" Annual Periodic Adverse Drug Experience Report, Special Pregnancy Report, and Program Evaluation Report will be submitted that covers the time period from the last report through December 30, 2005. Submit the Annual Periodic Adverse Drug Experience Report, the Psychiatric Quarterly Report, the Special Pregnancy Report, and the iPLEDGE Program Evaluation Report, including the "close-out" reports, to the Division of Dermatologic and Dental Drug Products and three copies of all the reports directly to:

Office of Drug Safety (HFD-400)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

FDA will re-evaluate the adequacy of the iPLEDGE program on a continuing basis regarding its success in achieving the goal of minimizing drug exposure during pregnancy and adherence to program components. Failure of iPLEDGE to achieve minimization of drug exposure during pregnancy, or failure to adhere to program components that may lead to pregnancy exposures, could lead to further regulatory action.

We agree that by November 12, 2005, Hoffman La-Roche will submit a Process Compliance Evaluation Plan designed to monitor, detect, and correct distribution outside the iPLEDGE program. FDA and Hoffman La-Roche have agreed that the Process Compliance Evaluation Plan will include the elements described in your submission of August 11, 2005, entitled "Agreements Needed for Compliance Evaluation Plan." The agreed upon plan will be implemented by January 1, 2006.

Pursuant to 21 CFR Part 208, FDA has determined that Accutane poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Accutane. FDA has determined that Accutane is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Accutane. In addition, patient labeling could help prevent serious adverse events related to use of the product.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted August 11, 2005 for the Package Insert, Patient Information/Informed Consents, and Medication Guide and for the blister card and carton labels. Marketing the product with FPL with text that is not identical to the approved text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 18-662/S-056**." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the labeling directly to:

Division of Drug Marketing, Advertising, and Communications (HFD-42)
Center for Drug Evaluation and Research
Food Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Florence Houn, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Florence Houn

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ACCUTANE RISK MINIMIZATION ACTION PLAN: SUMMARY of iPLEDGE

iPLEDGE is a performance-linked access system that, for female patients of childbearing potential, ties pregnancy testing results and Accutane prescription and dispensing. The iPLEDGE program is a computer-based Risk Minimization Action Plan (RiskMAP) that involves registration of wholesalers and registration and activation of pharmacies, prescribers, and patients to control distribution, dispensing, prescribing, and access to Accutane.

I. Prescribing Program
   A. General requirements: Hoffman La-Roche will ensure that the following requirements are addressed by its RiskMAP, iPLEDGE:
      1. Accutane must only be distributed by iPLEDGE registered wholesalers, dispensed by iPLEDGE registered and activated pharmacies, prescribed by iPLEDGE registered and activated prescribers, and prescribed/dispensed for iPLEDGE registered and activated patients. Wholesalers, prescribers, pharmacies, and patients may voluntarily terminate registration or deactivate from the iPLEDGE program at any time. Hoffman La-Roche may remove from the iPLEDGE program registered wholesalers and activated pharmacies and activated prescribers if agreed upon responsibilities are not met.
      2. For females of childbearing potential, Accutane must only be prescribed initially on confirmation of two negative pregnancy tests (one screening test conducted when the decision is made to pursue qualification of the patient for Accutane and a second confirmation test conducted at a CLIA-certified laboratory within seven days of the office visit). Subsequent prescriptions are contingent on confirmation of a monthly negative pregnancy test conducted at a CLIA-certified laboratory.
   B. Wholesaler registration: Hoffman la-Roche will accept registrations for iPLEDGE from wholesalers who agree to the following:
      1. To register prior to distributing Accutane and re-register annually thereafter.
      2. To distribute only FDA-approved Accutane product.
      3. To only ship Accutane to wholesalers registered in the iPLEDGE program with prior written consent from Hoffman La-Roche or pharmacies licensed in the U.S. and registered and activated in the iPLEDGE program.
      4. To notify Hoffman La-Roche (or delegate) of any non-registered and/or non-activated pharmacy or unregistered wholesaler that attempts to order Accutane.
      5. To comply with inspection of wholesaler records for verification of compliance with the iPLEDGE program by Hoffman La-Roche (or delegate).
      6. To return to the Hoffman La-Roche (or delegate) any undistributed product if registration is revoked by Hoffman La-Roche or if the wholesaler chooses to not reregister annually.
      7. To provide product flow data to Hoffman La-Roche (or delegate) as detailed in the wholesalers agreement.
   C. Pharmacy registration and activation:
      1. Hoffman La-Roche will accept registration for and activate into iPLEDGE only pharmacies that, through the designated Responsible Site Pharmacist (RSP), agree to the following:
         a. To attest to knowing the risk and severity of fetal injury/birth defects from Accutane.
         b. To train all pharmacists, who participate in the filling and dispensing of Accutane prescriptions, on the iPLEDGE program requirements.

c. To comply with the iPLEDGE program requirements, and seek to ensure all pharmacists who participate in the filling and dispensing of Accutane prescriptions comply with the iPLEDGE program requirements.
d. To obtain Accutane product only from iPLEDGE registered wholesalers.
e. To not sell, borrow, loan, or otherwise transfer Accutane in any manner to or from another pharmacy.
f. To return to Hoffman La-Roche (or delegate) any unused product if registration is revoked by Hoffman La-Roche or if the pharmacy chooses to not reactivate annually.
g. To not fill Accutane for any party other than a qualified patient.
h. To dispense only FDA-approved Accutane products
i. To not dispense or otherwise obtain Accutane product through the internet or any other means outside of the iPLEDGE program.
j. To re-activate annually

2. Hoffman La-Roche will only accept registration for and activation into iPLEDGE, pharmacies whose pharmacists that will dispense Accutane, agree to the following:
   a. To be trained by the RSP concerning the iPLEDGE program requirements.
   b. To obtain authorization from the iPLEDGE program via the internet or telephone for every Accutane prescription.
   c. To write the risk Management Authorization (RMA) number on the prescription.
   d. To comply with iPLEDGE dispensing requirements.
      i Dispense in no more than a 30-day supply.
      ii Dispense with an Accutane Medication Guide
      iii Dispense only after authorization from the iPLEDGE program.
      iv Dispense prior to the "do not dispense to a patient after" date provided by the iPLEDGE system.
      v Dispense only with a new prescription for refills and another authorization from the iPLEDGE program.

D. Prescriber registration and activation:
   1. Hoffman La-Roche will accept registration for and activation into iPLEDGE only prescribers who agree to activate their registration, and reactivate annually thereafter by attesting to the following:
      a. To possess specified skills and knowledge
      b. To comply with iPLEDGE program requirements.
      c. To counsel female patients of childbearing potential before beginning Accutane therapy and on a monthly basis, to avoid pregnancy by using two forms of contraception simultaneously and continuously one month before, during, and one month after Accutane therapy, unless the patient commits to continuous abstinence.
      d. To not prescribe Accutane to any female patient of childbearing potential until verifying that she has a negative screening pregnancy test and monthly negative CLIA-certified pregnancy tests as well as at the completion of therapy and one month later.
      e. To report any pregnancy case that occurs while a female patient is on Accutane and for one month after the last dose to the pregnancy registry.
      f. To obtain the patient's signed informed consent prior to prescribing Accutane.
   2. Hoffman La-Roche will accept registration for and activation into iPLEDGE only prescribers who agree to access the iPLEDGE system via the internet or telephone to:
      a. Register each patient in the iPLEDGE program.
      b. Confirm monthly that each patient has received counseling and education.

c. For female patients of childbearing potential:
   i Enter the patient's two chosen forms of contraception each month.
   ii Enter monthly results from CLIA-certified laboratory conducted pregnancy test.
d. Ensure that all patients, and specifically female patients of childbearing potential, meet the requirements to be registered and activated in the iPLEDGE program.

The tasks of counseling patients, obtaining informed consent, and obtaining and inputting patient registration information, pregnancy test results, and reported adverse events (including pregnancy exposures) may be delegated to qualified staff.

E. Patient registration and activation: Hoffman La-Roche will accept registration for and activation into iPLEDGE only patients who meet the following conditions:
   1. Must be registered with the iPLEDGE program by the prescriber.
   2. Must understand that severe birth defects can occur with the use of Accutane by female patients.
   3. Must be reliable in understanding and carrying out instructions.
   4. Must sign a "Patient Information/Informed Consent (for all patients)" form that contains warnings about the potential risks associated with Accutane.
   5. Must fill the prescription within seven days of the office visit.
   6. Must not donate blood while on Accutane and for one month after therapy has ended.
   7. Must not share Accutane with anyone.

   In addition to the requirements for all patients described above, female patients of childbearing potential must meet the following conditions:
   1. Must not be pregnant or breast-feeding.
   2. Must comply with the required pregnancy testing at a CLIA-certified laboratory.
   3. Must be capable of complying with the mandatory contraceptive measures for Accutane therapy, or commit to continuous abstinence from heterosexual intercourse, and understand behaviors associated with an increased risk of pregnancy.
   4. Must understand the responsibility to avoid pregnancy one month before, during, and one month after Accutane therapy.
   5. Must sign an additional "Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)" form, before starting Accutane therapy.
   6. Must access the iPLEDGE program via the internet or telephone before starting Accutane, on a monthly basis during therapy, and one month after the last dose to answer questions on the program requirements and to enter their two chosen forms of contraception.
   7. Must understand the purpose and importance of providing information to the iPLEDGE program should pregnancy occur while taking Accutane or within one month of the last dose.

II. Educational program: Hoffman La-Roche will implement an educational program for wholesalers, pharmacies, prescribers, and patients regarding the risks and benefits associated with the use of Accutane, education for contraception compliance, the requirements of the iPLEDGE program, and the requirements for interactions with the iPLEDGE program. Materials and proposals that address these educational requirements were submitted August 11, 2005 and include the following:

   A. Prescriber Educational Materials
      1. The iPLEDGE Program: Guide to Best Practices for Isotretinoin.
      2. Prescribing Checklist: First Office Visits for Females of Childbearing Potential.
      3. Prescribing Checklist: First Office Visits for Males and Females Who Cannot Get Pregnant.
      4. The iPLEDGE Program Contraception Referral Form and Contraception Counseling Guide.

5. The iPLEDGE Program: Prescriber Contraception Counseling Guide.
6. Recognizing Psychiatric disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin.

B. Pharmacy Educational Materials
1. The iPLEDGE Program: Pharmacist Guide for Isotretinoin

C. Patient Educational Materials
1. The iPledge Program: Patient Introductory Brochure
2. The iPLEDGE Program: Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant
3. The iPLEDGE Program: Guide to Isotretinoin for Female Patients Who Can Get Pregnant: The Importance of Avoiding Pregnancy on Isotretinoin
4. The iPLEDGE Program: Birth Control Workbook

D. Additional Information Sources:
1. iPLEDGE Information Internet Web Page
2. Call Center Support: A call center will be maintained to respond to healthcare practitioner, patient, pharmacist, and wholesaler questions and requests for information.

III. Reporting: Hoffman La-Roche will implement a reporting and collection system for: 1) serious adverse events associated with the use of Accutane that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81) and 2) for sales and dispensing of drug outside the iPLEDGE program. Reports will include the following:

A. 15-Day Adverse Event Reports: In addition to the postmarketing adverse events that meet the requirements for reporting under 21 CFR 314.80(c), the following will be reported as 15-Day Adverse Drug Experience Report:
1. All pregnancy exposures.
2. All psychiatric adverse events including suicides, attempted suicides, and suicidal ideation.

B. Periodic Adverse Drug Experience Reports
1. Narrative summary and analysis of information in the report.
2. Analysis by system organ class of the 15-Day Adverse Event Reports submitted in the preceding year.
3. Reports of adverse events not previously submitted as 15-Day Adverse Event Reports.
4. A history of action taken due to the occurrence of adverse events since the previous Periodic Adverse Drug Experience Report.

C. Psychiatric Quarterly Report: All psychiatric adverse events associated with the use of isotretinoin will be submitted quarterly as a supplementary report to the Periodic Adverse Drug Experience Report.

D. Special Pregnancy Quarterly Report: The following data will be submitted as a supplementary report to the Periodic Adverse Drug Experience Report.
a. All pregnancy exposures to Accutane in the U.S.
b. All cases of fetal malformation resulting from pregnancy exposure to Accutane in the U.S.
c. Copies of all 15-Day Adverse Event Reports for cases of pregnancy exposure to Accutane in the U.S. and fetal malformation resulting from Accutane exposure in the U.S.

E. Non-Compliant Distribution Reports: A description of all instances of sales and dispensing of Accutane product outside of the iPLEDGE program will be submitted within 15 days of Hoffman La-Roche's receipt of new information. Reports will include the following:

1. Information on the sale of any Accutane product by a wholesaler to an unregistered and/or un-activated pharmacy or unregistered wholesaler.
2. Information on dispensing of any Accutane product by an unregistered and/or un-activated pharmacy.
3. The details of the information to be submitted and the content, format, and frequency of the report will be agreed to by FDA.

IV. iPLEDGE Program Evaluation: Hoffman La-Roche, or their delegate, will conduct an evaluation of the effectiveness of the iPLEDGE program in minimizing drug exposure during pregnancy. The evaluation program will include the following:

A. Pregnancy Registry: Hoffman La-Roche will establish a pregnancy registry to actively collect information on any pregnancies occurring in female patients treated with Accutane. Paternal (exposed and non-exposed) cases will be excluded from the registry. The content, format, and frequency of reporting will be agreed to by FDA. The registry will be designed to incorporate the following:

1. Objectives
   a. Determine Accutane exposure status for each reported pregnancy.
   b. Document the outcome of each Accutane exposed pregnancy.
   c. Provide pregnancy documentation to assist in the evaluation, by root cause analysis, of iPLEDGE failures of each exposed pregnancy.
   d. Provide pregnancy data in periodic reports to FDA.
2. Outcome measures
   a. Pregnancy outcome.
   b. Congenital anomalies (major and minor birth defects).
   c. Other pregnancy or delivery complications or abnormalities.
   d. Neonate/infant outcomes.
   e. Infant follow-up for reports of fetal exposure.
3. Failure Mode and Effects Analysis Plan
   a. Hoffman La-Roche, or its delegate, will analyze the incidences of pregnancy in women exposed to Accutane. Analyses will include patient (monthly) assessments of the following:
      i Patient interaction with iPLEDGE to determine patient knowledge, attitudes, and behavior regarding iPLEDGE requirements.
      ii Patient acknowledgement of receipt of educational materials and contraceptive counseling.
   b. Hoffman La-Roche, or its delegate, will analyze the root cause for program failure for patients who become pregnant, including
      i Determination of patient knowledge, attitudes, and behavior regarding iPLEDGE requirements.
      ii Determination of the most likely cause of pregnancy.

B. iPLEDGE Process Compliance Evaluation Plan:
Hoffman La-Roche will submit a Process Compliance Evaluation Plan by November 12, 2005 designed to monitor, detect, and correct distribution outside the iPLEDGE program. FDA and Hoffman La-Roche have agreed that the Process Compliance Evaluation Plan will include the following elements as described in the submission dated August 11, 2005, entitled "Agreements Needed for Compliance Evaluation Plan." The agreed upon plan will be implemented by January 1, 2006.

1. Wholesaler Compliance: Hoffman La-Roche will:

a. Implement an evaluation plan, as agreed upon with FDA, to assess wholesaler compliance with the requirements of the iPLEDGE program and report on the data collected in a manner and at the frequency agreed upon with FDA.
b. Implement a corrective action plan, as agreed upon with FDA, to address wholesaler noncompliance with the iPLEDGE program.

2. Pharmacy Compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan, as agreed upon with FDA, to assess pharmacy compliance with the requirements of the iPLEDGE program and report on the data collected in a manner and at the frequency agreed upon with FDA.
   b. Implement a corrective action plan, as agreed upon with FDA, to address noncompliance with the iPLEDGE program.
3. Prescriber Compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan, as agreed upon with FDA, to assess prescriber compliance with the requirements of the iPLEDGE program and report on the data collected at the frequency agreed upon with FDA.
   b. Implement a corrective action plan to address prescriber noncompliance with iPLEDGE requirements.
4. Patient compliance: Hoffman La-Roche will:
   a. Implement an evaluation plan to assess patient compliance with iPLEDGE program requirements.
      i Independent Validation of iPLEDGE Patient Compliance: Hoffman La-Roche, or its delegate, will develop an independent means to audit patient compliance with the requirements of the iPLEDGE program and to report on the data collected at the frequency agreed upon with FDA.
      ii Evaluation of patients lost to follow-up or who discontinued Accutane: Hoffman La-Roche, or its delegate, will develop a method to allow evaluation of patients lost to follow-up or who discontinued Accutane to assess the reason(s) for no longer being in iPLEDGE.
   b. Implement a corrective action plan to address patient noncompliance with iPLEDGE.