



NDA 20-544/S-003

Population Council
Attention: Harold Nash, Ph.D.
Senior Scientist
1230 York Avenue
New York, NY 10021

Dear Dr. Nash,

Please refer to your supplemental new drug application dated September 25, 2000, received September 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Jadelle[®] (levonorgestrel) Implants.

We also acknowledge receipt of your submissions dated June 13 and 28, August 9, September 20, November 6, 8, 13 and 21, 2002.

Your submission of May 23, 2002 constituted a complete response to our July 24, 2001 action letter.

This supplemental new drug application proposes an extension of the approved duration of use of Jadelle[®] (levonorgestrel) Implants for the prevention of pregnancy from "up to 3 years" to "up to 5 years."

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert submitted November 20, 2002). Marketing the product with FPL that is not identical to the approved labeling text render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may 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. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-544/S-003." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing commitments in your submission dated November 21, 2002.

These commitments are listed below:

Chemistry

1. Certificates of analyses including analytical data of (b)----- from the 25 lots, described in the amendment submitted on November 8, 2002, along with a specification sheet will be provided to the FDA by December 8, 2002.
2. Before Jadelle[®] packages are distributed in the United States, a mock-up of the package labeling, including the stick-on labels identifying lot number will be submitted to the FDA for review, accompanied by two stick on labels identifying the lot number. They will be mounted on a sheet that instructs that one of the labels be transferred to the printed material that the patient takes home with her and the other be transferred to the patient record retained by the provider.

Clinical Pharmacology and Biopharmaceutics

1. To obtain *ex vivo* release rate information on explanted implants following removal and/or following five years of use and following contraceptive failure, as follows:
 - For each pair of explanted implants (after removal or five years of use from patients and at the time of contraceptive failure), you should subject one implant to a series of in vitro dissolution tests via 0.13% benzalkonium chloride medium, then 1.0% hydroxypropyl- β -cyclodextrin (HPBCD) and then in normal saline medium, and then assay for the amount of levonorgestrel remaining for each implant. For the other implant of the explanted pair, you should subject it to the same in vitro dissolution tests via normal saline medium first, then 1.0% HPBCD and then 0.13% benzalkonium chloride medium, and then assay for the amount of levonorgestrel remaining for each implant. Each dissolution test should last for 15 days. You should visually test the integrity of the explanted implants and record the explant conditions.
 - If you propose to conduct the above study using explanted Jadelle[®] units that have been stored, please provide data regarding the effect of storage on the dissolution of explanted rods.
 - You should also do the same sequence of in vitro dissolution tests (0.13% benzalkonium chloride – 1.0% HPBCD- normal saline, and normal saline – 1.0% HPBCD - 0.13% benzalkonium chloride) for unused Jadelle[®] at initial release, six months, and three years of storage.
 - The protocol for this study should be submitted to the Division within six months after the approval date and a final study report should be submitted within six months after completion of the study.
2. To continue to collect the *in vitro* release data in normal saline media to five years for three commercial production batches manufactured with (b)-----tubing.

Please be reminded also that the shelf-life of the drug product should not be extended without satisfactory stability data from three post approval production lots.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled “Postmarketing Study Protocol”, “Postmarketing Study Final Report”, or “Postmarketing Study Correspondence.”

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division, the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Karen Anderson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Physician Insert
Patient Package Insert

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/s/

Daniel A. Shames
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