DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-496-6411
FAX: 301-402-2071
E-mail: Lball@osophs.dhhs.gov

March 19, 2002

Wyatt R. Hume, D.D.S., Ph.D.
Executive Vice Chancellor
University of California Los Angeles
405 Hilgard Avenue
Los Angeles, CA 90095-1401

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1127

Research Project: **Study of the Effects of Estrogen Replacement Therapy on the Course of Depression and Cognitive Function in Perimenopausal Women**
Protocol Number: **UCLA IRB #00-10-027**
Principal Investigator: **Natalie Rasgon, M.D., Ph.D.**

Research Project: **Study of the Effects of Estrogen Replacement Therapy on the Course of Depression and Anxiety in Perimenopausal Women: A Pilot Study**
Protocol Number: **UCLA IRB #97-11-025-03**
Principal Investigator: **Natalie Rasgon, M.D., Ph.D.**

Dear Dr. Hume:

The Office for Human Research Protections (OHRP) has reviewed the University of California Los Angeles's (UCLA's) February 26, 2002 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding this research:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.116 and 46.117 stipulate that no investigator may involve a human subject in research unless the investigator has obtained and documented the legally effective informed consent of the subject, except under limited circumstances approved by the IRB. OHRP finds that screening procedures were performed for the above referenced research without the investigators obtaining and documenting the legally effective informed consent of the subjects. Specifically, OHRP notes that a "Perimenopause Screening Form" for the subject LR, was completed on **December 26, 2000** (UCLA's letter of February 26, 2002, Attachment C). This screening form recorded indentifiable private information including the subject's name, phone number, age, date of birth and information on her medical history. UCLA's letter of February 26, 2002 indicated that this screening was for a different IRB approved study, IRB #97-11-025-03, than for the study in which subject LR signed an informed consent document (IRB #00-010-027). However, UCLA has not provided documentation that the investigators obtained or documented informed consent from subject LR for study IRB #97-11-025-03 prior to the screening procedure. According to UCLA's report of October 9, 2001 and letter of February 26, 2002, informed consent was not obtained or documented from subject LR until **February 14, 2001**, well after screening was completed on December 26, 2000, with such informed consent obtained for study IRB #00-010-027.

Corrective action: OHRP finds that UCLA has developed and implemented satisfactory correction action plans to ensure that screening procedures are not performed prior to investigators obtaining and documenting the legally effective informed consent of subjects as appropriate under HHS regulations at 45 CFR 46.116 and 46.117. OHRP notes that the UCLA IRB Chairs developed and have distributed the guidance document "Informed Consent Procedures for Screening of Research Subjects and a template (UCLA report of October 9, 2001, Attachment E). In particular, OHRP notes the following:

(a) This guidance informs the UCLA research community that screening procedures that include data collection for the purposes of determining subject eligibility for research may require obtaining and documenting informed consent as defined under 45 CFR 46.116 and 46.117.

(b) The template script is used for oral informed consent via telephone screening that presents no more than minimal risk to subjects and is limited to questions that do not require signed consent outside of the research context.

(c) The IRB review of telephone screening instruments now requests that investigators modify their procedures to ensure that any waiver of the requirement for the investigator to obtain a signed consent document is in accordance with HHS regulations under 45 CFR 46.117(c)(2).

OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the UCLA MPA.

(2) HHS regulations at 45 CFR 46.115(a)(2) require that the informed consent document contain a description of the reasonably foreseeable risks and discomforts. OHRP finds that the informed consent document approved by the UCLA IRB on February 8, 2001 for study IRB #00-010-027 did not include a statement on the rare risk of endometrial cancer following use of Climara, the estrogen replacement therapy to be used in the study, although this risk was included in the 2001 Physicians' Desk Reference for Climara.

Corrective action: OHRP acknowledges UCLA's statement in its letter of February 26, 2002 that the informed consent document's omission of the rare risk of endometrial cancer following use of Climara was in error. OHRP notes that the investigator has closed the protocol and no subjects have received the study medications. If this study were to be reopened, OHRP recommends that the rare risk of endometrial cancer following use of Climara estrogen replacement therapy be included in IRB-approved informed consent document.

OHRP offers the following additional guidance:

(3) HHS regulations at 45 CFR 46.111(a)(6) require that in order to approve research covered by the regulations, the IRB shall determine, when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. OHRP notes that UCLA's letter of February 26, 2002 outlined general plans for monitoring adverse events in subjects. OHRP acknowledges that this study has been closed. If this study were to be reopened, OHRP recommends that the plans outlined in UCLA's letter of February 26, 2002 for monitoring the safety of subjects be included in both the IRB-approved protocol and informed consent documents; specifically, that the subjects will be monitored weekly via clinical evaluation by the investigator to assess potential adverse effects.

Finally, OHRP acknowledges the February 26, 2001 facsimile from Dr. Daniel Shames, Acting Director, Division of Reproductive and Urologic Drug Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, Food and Drug Administration who concluded that the above-referenced study, UCLA IRB #00-10-027, meets all of the requirements for exemption from IND regulations under 21 CFR 312(b)(4).

As a result of the above-referenced actions by UCLA, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter these determinations.

OHRP appreciates the continued commitment of your institution to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Leslie K. Ball, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Albert Carnesale, UCLA
Ms. Judith Brookshire, UCLA
Mr. Steven Peckman, UCLA
Dr. Carmine Clemente, UCLA
Dr. Robert Figlin, UCLA
Dr. Natalie Rasgon, UCLA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Dr. Kamal K. Mittal, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James McCormack, FDA