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: 301-435-0668
FAX: 301-402-2071
E-mail: pmcneilly@osophs.dhhs.gov

November 5, 2004

Cornelius W. Sullivan, Ph.D.
Vice Provost for Research
University of Southern California - Health Science
300 Bovard - University Park Campus
Los Angeles, CA 90089

Harry E. Douglas, III, D.P.A.
Interim President
Charles R. Drew University
School of Medicine and Science
1731 East 120th Street
Los Angeles, CA 90059

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 5906 and FWA 2736

Research Publication: **E.T. Schroeder et al, Effects of an Oral Androgen on Muscle and Metabolism in Older, Community-Dwelling Men. *Am. J. Physiol. Endocrinol. Metab.* 284: E120-E128, 2003.**

Dear Drs. Sullivan and Douglas:

The Office for Human Research Protections (OHRP) has reviewed the University of Southern California's (USC) August 21, 2003 report and Charles R. Drew University School of Medicine and Science's (CDU) August 25, 2003 and September 27, 2004 reports, submitted in response to OHRP's July 9, 2003 and August 11, 2004 letters regarding the above-referenced research.

Based upon its review of your reports, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the institutional review board

(IRB) at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chair or another IRB member designated by the chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied. After reviewing material submitted by CDU, OHRP found numerous instances in which the CDU IRB failed to conduct continuing review of research at least once per year.

OHRP notes that the IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or if the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

Corrective action: OHRP acknowledges that CDU has made changes to its system for the protection of humans subjects and will instruct its investigators to file continuing review applications at least eight weeks prior to the expiration date. CDU will also provide these instructions as part of training sessions and make this information available on its web site. In addition, in the event of a lapse in continuing review, the CDU IRB will request that investigators submit data collected during such a lapse to the IRB in an effort to ensure that the data is not used for research purposes.

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

(2) OHRP's July 9, 2003 letter to USC and CDU outlined the following allegations:

> (a) The investigators failed to conduct the above-referenced research using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, as required by HHS regulations at 45 CFR 46.111(a)(1).
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> (b) The investigators for the above-referenced research failed to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits, as required by HHS regulations at 45 CFR 46.111(a)(2).
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> (c) The investigators for the above-referenced research failed to ensure that the

selection of subjects is equitable, as required by HHS regulations at 45 CFR 46.111(a)(3).

(d) The investigators for the above-referenced research failed to ensure that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, as required by HHS regulations at 45 CFR 46.111(a)(6).

(e) The informed consent process for the research failed to include certain elements required by HHS regulations at 45 CFR 46.116.

(3) OHRP notes that the complaint outlined, among other things, the following specific points:

(a) The use of oxymetholone could cause a disruption of the hypothalamic-pituitary-testicular axis (HPTA), resulting in a state of hypogonadism. This was not taken into account when designing the research.

(b) No studies exist which describe the normalization of the HPTA and the extent of hypogonadism in subjects after androgen withdrawal. As a result, the risks to the subjects were not reasonable in relation to the anticipated benefits.

(c) The research failed to consider the possible adverse outcome of hypogonadism in the study design, and utilized a study population which may be more vulnerable to this condition.

(d) The investigators failed to monitor for total and free testosterone levels at the end of the 12-week treatment period, thus failing to monitor for a possible hypogonadal state in the subjects.

(e) The effect of oxymetholone on the HPTA and subsequent effects on gonadal function were not discussed in the design of the study. As a result, risks associated with hypogonadism were not included in the risks of the study as part of the informed consent process.

(4) OHRP notes the following points outlined in the USC and CDU responses to OHRP's July 9, 2003 letter:

(a) Hypogonadism was not a risk to the subjects while the study was in progress, since the subjects were receiving an androgen supplement.

(b) There was no reason to believe that hypogonadal symptoms would be expected, since:

(i) No similar studies reported evidence of hypogonadism after androgen cessation.

(ii) There is no evidence to suggest that normal testicular function did not recover quickly in subjects enrolled in the research, as supported by unpublished data.

(iii) The risk of hypogonadism is not listed as part of the Food and Drug Administration-approved labeling of oxymetholone.

(c) Previous studies have shown that testosterone administration to healthy young men resulted in increased muscle size and strength. However, previous studies on the effects of testosterone administration in older men were inconsistent. Since the subjects in the above-referenced research were community-dwelling men at risk of sarcopenia and frailty, they were an appropriate population for the study.

(d) Since the risk of hypogonadism had not been seen in similar previous studies using similar androgens, such risks were not required to be presented as part of the informed consent process. In addition, the informed consent document listed certain symptoms that are related to androgen administration and may also be associated with hypogonadism.

Based upon the information provided by USC and CDU, OHRP finds that the allegations listed under Item (2) above could not be substantiated. OHRP notes that an IRB could reasonably have made the determinations necessary for the approval of the research referenced above under HHS regulations at 45 CFR 46.111.

As a result of the determinations above, there should be no need for further involvement of OHRP in this matter. OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Diana Shycoff, IRB Director, USC Health Sciences Campus
Dr. Darcy Spicer, Chair, IRB and Assistant Dean for Clinical Studies, USC
Ms. Nancy Moody, Director, IRB, Charles R. Drew University (CDU)

Dr. Kenneth E. Wolf, Chair, IRB, CDU
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP