

Recombinant DNA Molecules (59 FR 34496 and 59 FR 40170).

**SUMMARY:** This notice sets forth an action to be taken by the Director, National Institutes of Health (NIH), under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496 and 59 FR 40170).

**FOR FURTHER INFORMATION CONTACT:** Additional information can be obtained from Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities (ORDA), Office of Science Policy and Technology Transfer, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838.

**SUPPLEMENTARY INFORMATION:** Today's action is being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules. This proposed action was published for comment in the **Federal Register** of February 8, 1995 (60 FR 7630), and reviewed and recommended for approval by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on March 6-7, 1995.

### **I. Background Information and Decisions on Actions Under the NIH Guidelines**

#### *A. Amendments to Sections I, III, IV, V, and Appendices C, F, G, I, and M of the NIH Guidelines Regarding Consolidated Review of Human Gene Transfer Protocols*

On July 18-19, 1994, the National Task Force on AIDS Drug Development held an open meeting for the purpose of identifying barriers to AIDS Drug Discovery that included a proposal to streamline the dual review process for human gene transfer experiments. Members of the Task Force recommended a consolidated review process to enhance interactions between the NIH and the Food and Drug Administration (FDA). As a result of the Task Force's deliberations, recommendations were adopted in order to eliminate any unnecessary overlap between the NIH and FDA review of human gene transfer proposals. Both Drs. Varmus and Kessler noted that their respective agencies would cooperate fully to effect the changes necessary to implement these recommendations.

The NIH and FDA proposed that the RAC become advisory to both the NIH Director and the FDA Commissioner with regard to the review of human gene transfer protocols. In the interest of maximizing the resources of both agencies and simplifying the method and period of review for research protocols involving human gene

transfer, the NIH and FDA should institute an interagency consolidated review process that incorporates the following principal elements:

(1) All human gene transfer protocols shall be submitted directly to the FDA. Submission will be in the format required by the FDA and the same format will be used by the RAC when public review is deemed necessary.

(2) Upon receipt, FDA review will proceed. The NIH/ORDA staff will simultaneously evaluate the protocol for possible RAC review.

(3) Factors which may contribute to the need for RAC review include: (a) New vectors/new gene delivery systems, (b) new diseases, (c) unique applications of gene transfer, and (d) other issues that require further public review.

(4) If either the NIH/ORDA or FDA decides that a proposal should be reviewed by the RAC, the proposal will be forwarded to the RAC primary reviewers immediately. Whenever possible, Principal Investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required. (RAC reviewed applications will be distributed to RAC members approximately four weeks prior to the next quarterly RAC meeting.)

(5) Semiannual data reporting procedures will remain the responsibility of NIH (ORDA). Semiannual data reports will be reviewed by the RAC in a public forum.

In a letter dated August 2, 1994, Dr. Nelson A. Wivel, Director, ORDA, NIH, provided the RAC with background information regarding the National Task Force on AIDS Drug Development meeting, and proposed amendments to Sections I, III, IV, V, and Appendices C, F, G, I, and M of the NIH Guidelines, to reflect the proposed consolidated review process. The revised review process was proposed as follows:

(1) Investigators will be required to submit all human gene transfer proposals directly to the FDA in the format required by the FDA; therefore, investigators will no longer be required to provide a separate submission to NIH/ORDA for RAC review. The FDA Division of Cellular and Gene Therapies will forward a copy of each submission to NIH/ORDA. Both the FDA Division of Cellular and Gene Therapies and NIH/ORDA will simultaneously evaluate each proposal for the necessity for RAC review. Whenever possible, the investigators will be notified within 15 working days following receipt of the submission regarding the necessity for RAC review.

(2) If either the NIH/ORDA or FDA decides that a proposal should undergo

RAC review, the proposal will be forwarded to the RAC primary reviewers immediately. Any protocol submitted less than 8 weeks before a RAC meeting will be reviewed at the following quarterly RAC meeting.

(3) The RAC will make recommendations regarding approval/disapproval of protocols, including any relevant stipulations, to the NIH Director. The NIH Director will review, approve, and transmit the RAC's recommendations/stipulations to the FDA Commissioner.

(4) The FDA will consider such recommendations/stipulations and will be responsible for completion of review. The RAC and NIH/ORDA will no longer have the responsibility for reviewing material submitted for Accelerated Review or for the review of minor modifications to human gene transfer protocols.

These proposed actions were discussed during the September 12-13, 1994, RAC meeting (published for public comments in the **Federal Register**, August 23, 1994 (59 FR 43426)). Dr. Philip Noguchi, Director, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, provided additional suggestions regarding the proposed review process including FDA adoption of the Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider), of the NIH Guidelines. The FDA will require investigators to submit the Points to Consider with their proposed experiments. A lengthy discussion ensued involving RAC members' concerns and suggestions regarding the consolidated review process.

Dr. Noguchi submitted the following compromise proposal regarding the NIH/FDA consolidated review of human gene transfer experiments:

(1) Appendix M, Points to Consider, will not be deleted from the NIH Guidelines. The NIH Guidelines will be modified to provide for submission of Appendix M, Points to Consider, directly to the FDA prior to IND submission. The FDA will update their guidance documents in a similar manner. When necessary, the RAC will continue to be responsible for modifying Appendix M, Points to Consider.

(2) The RAC, NIH/ORDA, and FDA will decide on the necessity for full RAC review. The submitted Appendix M, Points to Consider, will be publicly available for all human gene transfer