

on the protection of research subjects and have made participation in such programs a requirement for their investigators. Other sources of appropriate instruction might include the online tutorials offered by the Office of Human Subjects Research, NIH at <http://ohsr.od.nih.gov/>³ and by OHRP at <http://ohrp.osophs.dhhs.gov/educmat.htm>.⁴ Also, the University of Rochester has made available its training program for individual investigators. Its manual can be obtained through Centerwatch, Inc., at <http://www.centerwatch.com>.⁵ Within 30 days of the award, the principal investigator should provide a letter to the FDA grants management office which includes the names of the key personnel, the title of the human subjects protection education program completed by each named personnel, and a one-sentence description of the program. This letter should be signed by the principal investigator and co-signed by an institution official and sent to the Grants Management Officer.

C. Informed Consent

Consent forms, assent forms, and any other information given to a subject are part of the grant application and must be provided, even if in a draft form. The applicant is referred to DHHS regulations at 45 CFR 46.116 and 21 CFR 50.25 for details regarding the required elements of informed consent.

IV. Review Procedures and Criteria

A. Review Procedures

FDA grants management and program staff will review all applications sent in response to this notice. To be responsive, an application must be submitted in accordance with sections II.B, II.C, IV.B, and V of this document, and must bear the original signatures of both the principal investigator and the applicant institution's/organization's authorized official. Applications found to be nonresponsive will be returned to the applicant without further consideration. Applicants are strongly encouraged to contact FDA to resolve any questions about criteria before submitting their application. Please direct all questions of a technical or scientific nature to the OPD program staff and all questions of an administrative or financial nature to the grants management staff (see **FOR FURTHER INFORMATION CONTACT**).

Responsive applications will be reviewed and evaluated for scientific

and technical merit by an ad hoc panel of experts in the subject field of the specific application. Consultation with the proper FDA review division may also occur during this phase of the review to determine whether the proposed study will provide acceptable data that could contribute to product approval. Responsive applications will be subject to a second review by a National Advisory Council for concurrence with the recommendations made by the first-level reviewers, and funding decisions will be made by the Commissioner of Food and Drugs or his designee.

B. Program Review Criteria

1. Applications must propose clinical trials intended to provide safety and/or efficacy data of one therapy for one orphan indication.

2. There must be an explanation in the "Background and Significance" section of how the proposed study will either contribute to product approval or provide essential data needed for product development.

3. The prevalence, not incidence, of the population to be served by the product must be fewer than 200,000 individuals in the United States. The applicant should include, in the "Background and Significance" section, a detailed explanation supplemented by authoritative references in support of the prevalence figure. Diagnostic tests and vaccines will qualify only if the population of intended use is fewer than 200,000 individuals in the United States per year.

4. The study protocol proposed in the grant application must be under an active IND or IDE (not on clinical hold) to qualify the application for scientific and technical review. Additional IND/IDE information is described as follows:

- The proposed clinical protocol should be submitted to the FDA IND/IDE reviewing division a minimum of 30 days before the grant application deadline.

- The number assigned to the IND/IDE that includes the proposed study should appear on the face page of the application with the title of the project. The date the subject protocol was submitted to FDA for the IND/IDE review should also be provided.

- Protocols that would otherwise be eligible for an exemption from the IND regulations must be conducted under an active IND to be eligible for funding under this FDA grant program.

- If the sponsor of the IND/IDE is other than the principal investigator listed on the application, a letter from the sponsor permitting access to the IND/IDE must be submitted. Both the

principal investigator named in the application and the study protocol must have been submitted to the IND/IDE.

- Studies of already approved products, evaluating new orphan indications, are also subject to these IND/IDE requirements.

- Only medical foods that do not need premarket approval are free from these IND/IDE requirements.

5. The requested budget must be within the limits, either \$150,000 in direct costs for each year for up to 3 years for any phase study, or \$300,000 in direct costs for each year for up to 3 years for phase 2 or 3 studies. Any application received that requests support over the maximum amount allowable for that particular study will be considered nonresponsive.

6. Evidence that the product to be studied is available to the applicant in the form and quantity needed for the clinical trial must be included in the application. A current letter from the supplier as an appendix will be acceptable.

7. The narrative portion of the application (excluding appendices) should be no more than 100 pp., single-spaced, printed on 1 side, with 1/2-inch margins, and in unrounded 12-point font. The application should not be bound.

C. Scientific/Technical Review Criteria

The ad hoc expert panel will review the application based on the following scientific and technical merit criteria:

1. The soundness of the rationale for the proposed study.

2. The quality and appropriateness of the study design, including the design of data and safety monitoring plans.

3. The statistical justification for the number of patients chosen for the study, based on the proposed outcome measures and the appropriateness of the statistical procedures for analysis of the results.

4. The adequacy of the evidence that the proposed number of eligible subjects can be recruited in the requested timeframe.

5. The qualifications of the investigator and support staff, and the resources available to them.

6. The adequacy of the justification for the request for financial support.

7. The adequacy of plans for complying with regulations for protection of human subjects.

8. The ability of the applicant to complete the proposed study within its budget and within time limits stated in this request for applications (RFA).

A score will be assigned based on the scientific/technical review criteria. The review panel may advise the program

^{3,4,5} FDA has verified the Web site address, but we are not responsible for subsequent changes to the Web site after this document publishes in the Federal Register.