FAQ Concerning the Orphan Products Grants Program – Natural History Grants

A. General Information, Eligibility, and Requirements

What is the application submission deadline for the Natural History Grant?
The deadline for submissions is **January 10, 2019.**

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date. Applicants should be aware that on-time submission means that an application is submitted error free (of both Grants.gov and eRA Commons errors) by 11:59 PM Eastern Time on **January 10, 2019**.

Is a Letter of Intent required?
A Letter of Intent in not required, is non-binding, and does not enter into the review of a subsequent application. However, the information that it contains allows FDA staff to estimate the potential review workload and plan the review. No responsiveness decision will be made based on the letter of intent.

Prospective applicants are asked to submit the letter of intent with information contained in the RFA by 11:59 PM Eastern Time on **December 10, 2018**.

Who may apply for an Orphan Products Natural History Grant?
The grants are available to any foreign or domestic, public or private, for-profit or nonprofit entity (including state and local units of government). Federal agencies may not apply.

How much money is available for the Orphan Products Grants Program Natural History Grants?
OOPD intends to commit approximately $2 million to natural history grants in Fiscal Year 2019. Application budgets are not limited, but need to reflect the actual needs of the proposed project.

An applicant planning to submit a grant application with $500,000 or more in direct costs in any year is required to provide this notification in writing to the

FDA Orphan Products Grants Program Director at least 4 weeks prior to the application deadline (i.e., by **December 13, 2018** by 11:59 PM Eastern Time). The applicant must receive a letter in response from OOPD confirming approval to include in an appendix of the submitted grant application. Please see the following for more information: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental -instructions-forms-d.pdf

How many years of funding are available?
The scope of the proposed project should determine the project period. For prospective Natural History Studies the maximum project period is four (4) years. For retrospective Natural History Studies the maximum project period is two (2) years.

For those studies with an expected duration of more than 1 year, a second, third, or fourth year of noncompetitive continuation of support will depend on the following factors: (1) Performance during the preceding year; (2) compliance with regulatory requirements, as applicable; and (3) availability of Federal funds.

What types of studies qualify?
This funding opportunity announcement (FOA) is intended to support prospective or retrospective observational/non-interventional natural history studies with a substantial potential to further current or future product development. Natural History studies eligible for this funding opportunity will support studies that characterize the natural history of rare diseases/conditions with the goal of providing data by innovative means to facilitate medical product development for patients living with rare diseases where unmet needs exist. Therefore, natural history studies at various stages of product development and/or disease knowledge are encouraged. For example, there may already be products in the pipeline that are seeking to develop/validate biomarkers or clinical outcome measures. Alternatively, where diseases are less well-characterized, there may be need to evaluate the major functional limitations and manifestations of the disease or identify genotypic and phenotypic subpopulations. Higher priority will be given to efficient natural history studies where the study has a potential to exert a broad impact in advancing multiple rare diseases sharing a similar pathophysiology.

Use of innovative models of natural history studies is highly encouraged under this FOA. Applications that propose simulations and modeling towards the study of safety and effectiveness of a product in conjunction with the natural history study will be a priority. Modeling and simulation allow for organization of diverse data sets, optimization of product dosing based on individual physiology and genetics, and can provide a vital tool to help evaluate new treatments in rare diseases where patient populations are inherently difficult to study because of their small size. Innovative methods for data collection as well as data dissemination which can serve as a model for future studies is also highly encouraged.

Do I need an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) to qualify for an Orphan Products Natural History grant?
No. An IND or IDE is not required for a natural history study to be qualified. However, if an IND or IDE is associated with the natural history study, we highly recommend that the IND or IDE number be provided in the application.

Can the proposed study include research being performed at foreign sites? Can all or part of the funding be used to support foreign clinical study sites?
Yes. The grants are available to any foreign or domestic, public or private, for-profit or nonprofit entity (including State and local units of government).

Foreign applications must indicate how the proposed project has specific relevance to the mission and objectives of FDA and has the potential for significantly advancing sciences in the United States.

Do I need a Federal Wide Assurance (FWA) for all foreign and domestic study sites?
Yes. All institutions engaged in human subject research financially supported by HHS must file an assurance of protection for human subjects with the Office of Human Research Protections (OHRP) (45 CFR part 46). Applicants are advised to visit the OHRP Web site for guidance on human subject protection issues. Federal regulations (45 CFR 46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

The requirement to file an assurance applies to both awardee and collaborating performance site institutions. Awardee institutions are automatically considered to be engaged in human subject research whenever they receive a direct HHS award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears the responsibility for protecting human subjects under the award.

The awardee institution is also responsible for, among other things, ensuring that all collaborating performance site institutions engaged in the research hold an approved assurance prior to their initiation of the research. No awardee or performance site institution may spend funds on human subject research or enroll subjects without the approved and applicable assurance(s) on file with OHRP. An awardee institution must, therefore, have its own IRB of record and assurance. The IRB of record may be an IRB already being used by one of the performance sites, but it must specifically be registered as the IRB of record with OHRP.

For further information, applicants should review the section on human subjects in the application instructions as posted on the Grants.gov application web site. For studies involving clinical protocol, the clinical protocol should comply with ICHE6 Good Clinical Practice Consolidated Guidance which sets an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

Do I need Institutional Review Board (IRB) approval at time of submission of grant application?
IRB approval is not required at the time of the submission of grant application although documentation of IRB approval for the IRB of record must be on file with the FDA grants management office before an award to fund the study will be made.

Should the protocol and informed consent forms be included in the grant application?
Yes. The protocol should be submitted in the application as an appendix. Informed consent and assent forms should be provided as an appendix as well

How and where do I submit my application?
All applications must be submitted electronically through Grants.gov. The applications must be prepared using the SF424 (R&R) application forms along with the SF424 (R&R) Application Guide for this funding opportunity as well as any program-specific instructions. Please use the link from the Orphan Products Natural History Grants Program website to the current NIH Guide for Receipt Dates and follow the Required Application Instructions in the Detailed RFA.

The earliest submission date for the RFA is November 10, 2018. The application submission deadline for the RFA is January 10, 2019 by 11:59 PM Eastern Time. A letter of intent is required a minimum of 30 days prior to the application due date (i.e. by December 10, 2018).

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date. Applicants should be aware that on-time submission means that an application is submitted error free (of both Grants.gov and eRA Commons errors) by 11:59 PM Eastern Time on the application due date. Late applications will not be accepted for this funding opportunity.

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B. Application Review Process and Timelines

How are applications reviewed?
FDA grants management and program staff will review all applications. To be

responsive, an application must be submitted in accordance with the requirements of the Request for Applications (RFA). Applications found to be non-responsive will be returned to the applicant without further consideration. Responsive applications will be reviewed and evaluated for scientific and technical merit by a panel of experts in natural history studies and in the subject field of the specific application. A score will be assigned to each application based on the scientific/technical review criteria. The review panel may advise the program staff about the appropriateness of the proposal to the goals of the grant program.

What criteria are considered for the application review?
Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Reviewers will consider each of the review criteria below in the determination of scientific merit.

1. Rationale:
The soundness of rationale in relation to the current understanding of the rare disease(s) and the likelihood the proposal will facilitate medical product development to address an unmet medical need in a rare disease(s) or provide highly significant improvements in treatment or diagnosis and assist or substantially contribute to market approval of product(s).

2. Study Design and Inclusion of Patient Input:
The quality and appropriateness of the study design, research methodology, data and data analyses to accomplish the specific aims of the proposed study. Patients and caregivers should be involved in the planning of the design and development of these studies. Their unique insights and experiences to provide data about the natural progression of the disease to inform rare disease medical product development programs.

3. Investigator(s):
The qualifications of the Principal Investigator(s) (PIs), collaborators, and other support staff.

4. Infrastructure and Resources:
The probability of success of the proposed project given the environment in which the work will be done.

5. Ability to Advance the Current Field:
The ability of the project to advance current research or clinical practice paradigms towards future product development and to exert a significant influence on product development.

In addition, reviewers will evaluate the following additional items while determining scientific and technical merit:

- Budget and Period of Support
- Protections for Human Subjects
- Inclusion of Women, Minorities, and Children
- Resource Sharing Plans
- Foreign Organizations
- Biohazards

See the RFA for further information.

When will I be notified of the review results?
Applicants will usually be notified of the review results via a summary statement approximately 6 months from the application deadline.

How and when are grant funds distributed?
Once the grant applications are reviewed and scored by the panel of experts, a cut-off score for funding will be established. Those applications within the anticipated fundable range will be ranked in order of their score with the earliest possible funding start date beginning August 2019 based on availability of funds.
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C. Post-Award Responsibilities

What happens after the grant review is completed?
All responsive applications will be issued scores and summary statements following the review of the applications. If your grant application received a favorable/competitive score you will be sent a cover memo and a Pre-Funding Certification Form (PCF) along with a copy of the Summary Statement. You will be required to complete and return the PCF and accompanying information (including your responses to the Summary Statement critiques, the current IRB approval letter, Federal Wide Assurance documentation and verification of product availability) by the date specified in the cover memo. This is not a guarantee that you will receive funding.

Who will be my main contact within the Office of Orphan Products Development (OOPD) when I receive grant funding?
If you receive grant funding, you will receive a formal Notice of Grant Award. Your grant will be assigned an OOPD grant Project Officer (PO) who will be your main contact. You will be required to keep the PO informed throughout the grant of any issues and changes including protocol changes, adverse events, changes in key study personnel, etc. If you have any questions or concerns about the grant or the study, you may contact the PO for assistance. Additionally, if you experience any difficulties in patient enrollment, OOPD may be able to assist or suggest options.

After I receive grant funding, what can I expect as a grantee?
You will receive a congratulatory letter from the PO outlining your roles, responsibilities, and requirements as a grantee. You will be required to follow and be in compliance with Good Clinical Practices and Current Good Manufacturing Practices as applicable. You will be required to maintain regulatory requirements such as IRB approvals, up to date FWA, IND requirements (as applicable) including submission of IND annual reports and appropriate adverse event reporting, up to date clinicaltrials.gov information (for applicable or voluntarily registered trials), etc. To assist in monitoring your grant, your PO will establish enrollment and progress goals for each funding year with you upon initial funding. You will also be required to submit Quarterly Reports and Annual Reports to OOPD. There will be at least one grant evaluation with OOPD during the lifetime of your grant. OOPD should be contacted before any protocol changes are made (including Key Personnel and Performance Site changes). Publication of study results is encouraged.

What reports will be required once my grant is funded?
Once the grant is funded, Quarterly Reports will be required typically every three months from the date the grant was issued. These reports should include an update on the overall progress of the study, monitoring of the study, and for "applicable clinical trials" and voluntarily registered trials an update on the ClinicalTrials.gov entry for the study. Additional information that should be reflected in these updates include enrollment, adverse events, changes in protocol, publications, and presentations.

In addition, an Annual Report in the form of a Research Performance Progress Report (RPPR) is required.

At the end of the grant, a Final Report will be due within 90 days after the end date of the project period.
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D. Contact Information

Who can I contact for questions concerning the budget of my potential grant application or funded grant?
Questions regarding financial aspects of a proposed application should be addressed to:
Daniel Lukash, FDA/Office of Acquisitions & Grant Services
Telephone: 240-402-7596
E-mail: Daniel.Lukash@fda.hhs.gov

Who can I contact for questions regarding the research/clinical protocol sections of my potential grant application?
Scientific and Research questions should be addressed to:
Katherine Needleman, FDA/Office of Orphan Products Development

Telephone: 301-796-8660
E-mail: Katherine.Needleman@fda.hhs.gov

Who can I contact for questions regarding technical issues with submitting the grant application?
Technical questions regarding submitting through grants.gov should be submitted to:

- eRA Service Desk *(Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)*
    - Finding Help Online: https://grants.nih.gov/support/index.html
    - Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

- Grants.gov Customer Support *(Questions regarding Grants.gov registration and submission, downloading forms and application packages)*
    - Contact Center Telephone: 800-518-4726
    - Email: support@grants.gov