Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	U.S. Food and Drug Administration (FDA) The FDA does not follow the NIH Page Limitation Guidelines or the NIH Review Criteria. Applicants are encouraged to consult with FDA Agency Contacts for additional information regarding page limits and the FDA Peer Review Process.
Components of Participating Organizations	Office of Orphan Products Development (OPD)
Funding Opportunity Title	**Clinical Studies of Safety and Effectiveness of Orphan Products Research Project Grant (R01)**
Activity Code	R01 Research Project Grant
Announcement Type	Reissue of RFA-FD-13-001
Related Notices	None
Funding Opportunity Announcement (FOA) Number	**RFA-FD-15-001**
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.103
Funding Opportunity Purpose	The goal of FDA's OPD grant program is to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the product being developed will be superior to the existing therapy. FDA provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. Applicants must include in the application's Background and Significance section documentation to support the assertion that the orphan disease or condition to be studied is a "rare disease or condition" and an explanation of how the proposed study will either help support product approval or provide essential data needed for product development.

Key Dates

Posted Date	
Open Date (Earliest Submission Date)	December 4, 2014
Letter of Intent Due Date(s)	Not Applicable.
Application Due Date(s)	Application Due Date(s): February 4, 2015; February 3, 2016; February 1, 2017; February 7, 2018 by 11:59 PM Eastern Time. Resubmission Due Date(s): October 15, 2015; October 14, 2016; October 16, 2017; October 15, 2018) by 11:59 PM Eastern Time. 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. This FOA uses non-standard due dates. See Receipt, Review and Anticipated Start Dates.

AIDS Application Due Date(s)	Not Applicable.
Scientific Merit Review	May 2015, 2016, 2017, and 2018 and November 2015, 2016, 2017, and 2018
Advisory Council Review	September 2015, 2016, 2017, and 2018 and February 2016, 2017, 2018, and 2019)
Earliest Start Date	November 2015, November 2016, November 2017, November 2018
Expiration Date	February 8, 2018, October 16, 2018 resubmission
Due Dates for E.O. 12372	Not Applicable

Required Application Instructions

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, **except where instructed to do otherwise.** Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

NOTICE: Applications submitted in response to this Funding Opportunity Announcement (FOA) for Federal assistance must be submitted electronically through Grants.gov (http://www.grants.gov) using the SF424 Research and Related (R&R) forms and the SF424 (R&R) Application Guide.

APPLICATIONS MAY NOT BE SUBMITTED IN PAPER FORMAT.

This FOA must be read in conjunction with the application guidelines included with this announcement in Grants.gov/Apply for Grants (hereafter called Grants.gov/Apply).

A registration process is necessary before submission and applicants are highly encouraged to start the process at least four (4) weeks prior to the grant submission date. See Section IV.

Table of Contents

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Background

The OPD was created to identify and promote the development of orphan products. Orphan products are drugs, biologics, medical devices, and medical foods that are indicated for a rare disease or condition. The term “rare disease or condition” is defined in 21 U.S.C. 360ee. As a practical way to implement the statutory definition, for devices and foods as well as for drugs, FDA considers drugs, devices, and medical foods potentially eligible for grants under the OPD grant program if they are indicated for a disease or condition that has a prevalence, not incidence, of fewer than 200,000 people in the United States. Diagnostics and vaccines are considered potentially eligible for such grants only if the U.S. population to whom they will be administered is fewer than 200,000 people in the United States per year.

Research Objectives

The goal of FDA's OPD grant program is to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the proposed product will be superior to the existing therapy. FDA provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. Applicants must include in the application's Background and Significance section documentation to support that the estimated prevalence of the orphan disease or condition in the United States is less than 200,000 (or in the case of a vaccine or diagnostic, information to support that the product will be administered to fewer than 200,000 people in the United States per year),and an explanation of how the proposed study will either help support product approval or provide essential data needed for product development. Additional information may be required upon request, for example, regarding population estimate and rationale. This additional information may be required, in part, to assure that human clinical trials of drugs are eligible to receive funding under the OPD grant program. 21 U.S.C. 360ee(b)(1)(A).See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Section II. Award Information

Funding Instrument	Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.

Application Types Allowed	New Renewal Resubmission Revision Note about Resubmissions: Applicants may submit a resubmission application, but such application must include an Introduction addressing the most recent objective review critique (Summary Statement). Summary Statements must be included as an appendix in the application. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-003.html and NOT-OD-09-016. The OER Glossary and the SF424 (R&R) Application Guide provide details on these application types.
Funds Available and Anticipated Number of Awards	Office of Orphan Products Development intends to commit $14.1 million in FY2016, FY2017, FY2018, and FY2019. Of the estimated FY 2016 funding ($14.1 million), approximately $10 million will fund non-competing continuation awards, and approximately $4.1 million will fund 5 to 10 new awards, subject to availability of funds. It is anticipated that funding for the number of non-competing continuation awards and new awards in FY 2017, FY 2018 and FY 2019 will be similar to FY 2016.
Award Budget	Phase 1 studies are eligible for grants of up to $250,000 per year for up to 3 years. Phase 2 and 3 studies are eligible for grants of up to $500,000 per year for up to 4 years. Please note that the dollar limitation will apply to total costs (direct plus indirect). Budgets for each year of requested support may not exceed the $250,000 or $500,000 total cost limit, whichever is applicable. The following definitions are provided to illustrate drug and biologic products study phases. Devices and medical foods may have alternative considerations. Phase 1 studies include the initial introduction of an investigational new drug (IND) into humans, are usually conducted in healthy volunteer subjects, and are designed to determine the metabolic and pharmacological actions of the product in humans, and the side effects associated with increasing drug doses to obtain data on the safety of the product. In some Phase 1 studies that include subjects with the rare disorder, it may also be possible to gain early evidence on effectiveness. Phase 2 studies include early controlled clinical studies conducted to: (1) Evaluate the effectiveness of the product for a particular indication in patients with the disease or condition and (2) determine the common short-term side effects and risks associated with it. Phase 3 studies generally gather more information about effectiveness and safety that is necessary to evaluate the overall risk-benefit ratio of the product and to provide an acceptable basis for product labeling.

Award Project Period	The length of support will depend on the nature of the study. 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 of IND/investigational device exemption (IDE), if applicable; and (3) availability of Federal funds. In addition to the requirement for an active IND/IDE discussed in Section V.3 of this document, documentation of assurances with the Office of Human Research Protection (OHRP) (see Section IV.5.A of this document) must be on file with the FDA grants management office before an award is made. Any institution receiving Federal funds must have an institutional review board (IRB) of record even if that institution is overseeing research conducted at other performance sites. To avoid funding studies that may not receive or may experience a delay in receiving IRB approval, documentation of IRB approval and Federal Wide Assurance (FWA or assurance) for the IRB of record for all performance sites must be on file with the FDA grants management office before an award to fund the study will be made. In addition, if a grant is awarded, grantees will be informed of any additional documentation that should be submitted to FDA's IRB. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the FDA provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds. FDA grants policies as described in the HHS Grants Policy Statement http://www.hhs.gov/grantsnet/adminis/gpd/index.htm will apply to the applications submitted and awards made in response to this FOA.

FDA grants policies as described in the HHS Grants Policy Statement will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for FDA support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)

- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education
- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations
- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments
- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- U.S. Territory or Possession

Other
- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

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 that are not part of the Department of Health and Human Services (HHS) may apply. Agencies that are part of HHS may not apply. For-profit entities must commit to excluding fees or profit in their request for support to receive grant awards. Organizations that engage in lobbying activities, as described in section 501(c)(4) of the Internal Revenue Code of 1968, are not eligible to receive grant awards.

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. Failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
    - NATO Commercial and Government Entity (NCAGE) Code – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons - Applicants must have an active DUNS number and SAM registration in order to

complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.

- Grants.gov – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))
All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 4-6 weeks prior to the application due date.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for support. The Project Director/Principal Investigator (PD/PI) will be solely responsible for planning, directing, and executing the proposed project.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

Multiple PDs/PIs
The decision of whether to apply for a grant with a single PD/PI or multiple PDs/PIs grant is the responsibility of the investigators and applicant organizations and should be determined by the scientific goals of the project. Applications for grants with multiple PDs/PIs will require additional information, as outlined in the instructions below. More than one PD/PI (i.e., multiple PDs/PIs), may be designated on the application for projects that require a team science approach and therefore clearly do not fit the single-PD/PI model. Additional information on the implementation plans and policies and procedures to formally allow more than one PD/PI on individual research projects is available at http://grants.nih.gov/grants/multi_pi.

When multiple PDs/PIs are proposed, FDA requires one PD/PI to be designated as the "Contact PI, who will be responsible for all communication between the PDs/PIs and the FDA, for assembling the application materials outlined below, and for coordinating progress reports for the project. The contact PD/PI must meet all eligibility requirements for PD/PI status in the same way as other PDs/PIs, but has no other special roles or responsibilities within the project team beyond those mentioned above.

Information for the Contact PD/PI should be entered in item 15 of the SF424 (R&R) Cover component. All other PDs/PIs should be listed in the Research & Related Senior/Key Person component and assigned the project role of PD/PI. Please remember that all PDs/PIs must be registered in the eRA Commons prior to application submission. **The Commons ID of each PD/PI must be included in the Credential field of the Research & Related Senior/Key Person component. Failure to include this data field will cause the application to be rejected.** All projects proposing Multiple PDs/PIs will be required to include a new section describing the leadership plan approach for the proposed project.

Multiple PD/PI Leadership Plan
For applications designating multiple PDs/PIs, a new section of the research plan, entitled Multiple PD/PI Leadership Plan [Section 14 of the Research Plan Component in the SF424 (R&R)], must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance

and organizational structure of the leadership team and the research project should be described, and should include communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Award (NoA).

Applications Involving a Single Institution
When all PDs/PIs are within a single institution, follow the instructions contained in the SF424 (R&R) Application Guide.

Applications Involving Multiple Institutions
When multiple institutions are involved, one institution must be designated as the prime institution and funding for the other institution(s) must be requested via a subcontract to be administered by the prime institution. When submitting a detailed budget, the prime institution should submit its budget using the Research & Related Budget component. All other institutions should have their individual budgets attached separately to the Research & Related Subaward Budget Attachment(s) Form. See Section 4.8 of the SF424 (R&R) Application Guide for further instruction regarding the use of the subaward budget form.

2. Cost Sharing

This grant program does not require cost sharing as defined in the HHS Grants Policy Statement.

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The FDA will not accept any application that is essentially the same as one currently pending initial objective review unless the applicant withdraws the pending application. FDA will not accept any application that is essentially the same as one already reviewed.

Section IV. Application and Submission Information

To comply with the President's Management Agenda, HHS is participating as a partner in the government-wide grants.gov application site. Applicants should apply electronically by visiting the web site www.grants.gov and following instructions under Apply for Grants. Users of grants.gov will be able to download a copy of the application package, complete it offline, and then upload and submit the application via the grants.gov web site. We strongly encourage using the Tips posted on www.grants.gov under the announcement number when preparing your submission. This process is similar to the R01 Grant Application process currently used at the National Institutes of Health (NIH). You can visit the following website for helpful background on preparing to apply, preparing an application, and submitting an application to Grants.gov: http://era.nih.gov/ElectronicReceipt/. In order to apply electronically, the applicant must have a Data Universal Number System (DUNS) number, and register in the System for Award Management (SAM) database, in eRA Commons (http://era.nih.gov/ElectronicReceipt/preparing.htm), and in grants.gov (further information below).

To download a SF424 (R&R) Application Package and SF424 (R&R) Application Guide for completing the SF424 (R&R) forms for this FOA, link to http://www.grants.gov/applicants/apply_for_grants.jsp and follow the directions provided on that web site.

A one-time registration is required for institutions/organizations at both:
Grants.gov (http://www.grants.gov/applicants/get_registered.jsp)

and
eRA Commons (http://era.nih.gov/ElectronicReceipt/preparing.htm)

A registration process with Grants.gov and eRA Commons is necessary before submission and applicants are highly encouraged to start the process at least four weeks prior to the grant submission date. PDs/PIs should work with their institutions/organizations to make sure they are registered in the eRA Commons.

Several additional separate actions are required before an applicant institution/organization can submit an electronic application, as follows:

1) Organizational / Institutional Registration in Grants.gov / Get Registered

- Your organization will need to obtain a DUNS number (http://fedgov.dnb.com/webform) and register with System for Award Management (SAM) as part of the Grants.gov registration process.
- The DUNS number is a 9-digit identification number that uniquely identifies business entities.
- The SAM database is a government-wide warehouse of commercial and financial information for all organizations conducting business with the Federal Government. SAM integrates the eight current federal procurement systems and the Catalog of Federal Domestic Assistance into a single new, streamlined system. This now houses the CCR system.
- If your organization does not have a Taxpayer Identification Number (TIN) or Employer Identification Number (EIN), allow for extra time. A valid TIN or EIN is necessary for SAM registration.
- The SAM also validates the EIN against Internal Revenue Service records, a step that will take an additional one to two business days.

Direct questions regarding Grants.gov registration can be directed to:
Grants.gov Customer Support
Contact Center Phone: 800-518-4726
Web ticketing system: https://grants-portal.psc.gov/ContactUs.aspx
Email support@grants.gov

Registration steps, in detail, can be found at
http://www07.grants.gov/applicants/organization_registration.jsp.

2) Organizational / Institutional Registration in the eRA Commons (https://commons.era.nih.gov/commons/registration/registrationInstructions.jsp)

- To find out if an organization is already Commons-registered, see the "List of Grantee Organizations Registered in eRA Commons. (http://era.nih.gov/userreports/ipf_com_org_list.cfm)
- Direct questions regarding the Commons registration can be directed to:
  eRA Commons Help Desk
  Phone: 301-402-7469 or 866-504-9552 (Toll Free)
  Finding Help Online: http://grants.nih.gov/support/index.html
  Email commons@od.nih.gov

3) Project Director / Principal Investigator (PD / PI) Registration in the eRA Commons: Refer to the eRA Commons System (COM) Users Guide.

- The individual(s) designated as PDs/PIs on the application must also be registered in the eRA Commons. In the case of multiple PDs/PIs, all PDs/PIs must be registered in the eRA Commons prior to the submission of the application.
- Each PD/PI must hold a PD/PI account in the Commons. Applicants should not share a Commons account for both an Authorized Organization Representative/Signing Official (AOR/SO) role and a PD/PI role; however, if they have both a PD/PI role and an Internet Assisted Review (IAR) role, both roles should exist under one Commons account. When multiple PDs/PIs are proposed, all PDs/PIs at the applicant organization must be affiliated with that organization. PDs/PIs located at

another institution need not be affiliated with the applicant organization, but must be affiliated with their own organization to be able to access the Commons.
- This registration/affiliation must be done by the AOR/SO or their designee who is already registered in the Commons.
- Both the PD/PI(s) and AOR/SO need separate accounts in the eRA Commons since both are authorized to view the application image. Note that if a PD/PI is already registered in the eRA Commons, another registration to apply for an FDA opportunity is not necessary.

Several of the steps of the registration process could take four weeks or more. Therefore, applicants should immediately check with their business official to determine whether their organization/institution is already registered in both Grants.gov and the Commons (https://commons.era.nih.gov/commons/). The FDA will accept electronic applications only from organizations that have completed all necessary registrations. Registration steps, in detail, can be found at https://commons.era.nih.gov/commons/registration/registrationInstructions.jsp.

If you experience **technical difficulties** with your online submission, you should contact the Grants.gov Customer Response Center http://www.grants.gov/contactus/contactus.jsp. If the Customer Response Center is unable to resolve your problem, please contact Vieda Hubbard, Grants Management Specialist, Division of Acquisition Support and Grants (DASG), Office of Acquisition and Grant Services (OAGS), Food and Drug Administration, at 240-402-7588, or by e-mail at vieda.hubbard@fda.hhs.gov.

1. Requesting an Application Package

Applicants must download the SF424 (R&R) application package associated with this funding opportunity using the "Apply for Grant Electronically" button in this FOA or following the directions provided at Grants.gov.

In FY 2016, 2017, 2018, and 2019 all applications must be submitted electronically through Grants.gov. Applicants must download the SF424 (R&R) application forms and the SF424 (R&R) Application Guide for this FOA through http://www.grants.gov/applicants/apply_for_grants.jsp.

Note: Only the forms package directly attached to a specific FOA can be used. You will not be able to use any other SF424 (R&R) forms (e.g., sample forms, forms from another FOA). **Please locate the current package each cycle to obtain the most up to date forms to download and submit.** Forms may change between receipt dates.

For further assistance, contact: Vieda Hubbard at 240-402-7588. Telecommunications for the hearing impaired: 301-480-0434.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications.

Prepare all applications using the SF424 (R&R) application forms and in accordance with the SF424 (R&R) Application Guide for this FOA through http://www.grants.gov/applicants/apply_for_grants.jsp.

The SF424 (R&R) Application Guide is critical to submitting a complete and accurate application to FDA. Some fields within the SF424 (R&R) application components, although not marked as mandatory, are required by FDA (e.g., the Credential log-in field of the Research & Related Senior/Key Person Profile component must contain the PD/PIs assigned eRA Commons User ID). Agency-specific instructions for such fields are clearly identified in the Application Guide. For additional information,

see Frequently Asked Questions Application Guide, Electronic Submission of Grant Applications (http://grants.nih.gov/grants/ElectronicReceipt/faq_full.htm#application).

Special instructions for applicants who are submitting a renewal or revision
Applicants submitting a renewal or resubmission are required to enter the previous grant number into the Federal Identifier field in the SF424 (R&R) Cover Component form (box #8). Renewal and resubmission applications that do not include this number will receive an error message. Applicants should log on to the eRA Commons to obtain the previous grant number. If the number is not available in Commons, contact Vieda Hubbard, 240-402-7588 at FDA to get the previous grant number in order to submit the application.
Visit http://era.nih.gov/ElectronicReceipt/resubmission_FAQ.htm for additional information. If an application for the same study was submitted in response to a previous request for application (RFA) but has not yet been funded, an application in response to this notice will be considered a request to withdraw the previous application. The applicant for a resubmitted application should address the issues presented in the summary statement from the previous review and **include a copy of the summary statement itself as part of the resubmitted application.** A resubmission application should be complete and stand alone from previous versions. An application that has received two prior disapprovals is not eligible for resubmission.

Prepare all applications using the SF424 (R&R) application forms and in accordance with the SF424 (R&R) Application Guide for this FOA through http://www.grants.gov/applicants/apply_for_grants.jsp. **Please locate the current package each cycle to obtain the most up-to-date forms to download and submit.** Forms may change between receipt dates.

Note that the move to electronic applications has brought a change in terminology. The Grants.gov terminology is as follows:

New = New
Resubmission = A Revised or Amended application
Renewal = Competing Continuation
Continuation = Noncompeting Progress Report
Revision = Competing Supplement

Letter of Intent
A letter of intent is not required for the funding opportunity.

Page Limitations
All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed, with the following exceptions or additional requirements:
- For this specific FOA, the Research Strategy section is limited to 25 pages.
- See the following for page instructions: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm186346.htm

Instructions for Application Submission
The forms package associated with this FOA includes all applicable components, mandatory and optional. The SF424 (R&R) application has several components. Some components are required, others are optional. The forms package associated with this FOA in http://www.grants.gov/applicants/apply_for_grants.jsp includes all applicable components, required and optional. Follow all instructions in the SF424 (R&R) Application Guide to ensure you complete all appropriate “optional” components. A completed application in response to this FOA includes the data in the following components:

Required Components:
SF424 (R&R) Cover
SF424 (R&R) Project/Performance Site Locations
SF424 (R&R) Other Project Information

SF424 (R&R) Senior/Key Person Profile
PHS398 Cover Page Supplement
PHS398 Research Plan
PHS398 Checklist
PHS398 Research & Related Budget
Research & Related Subaward Budget Attachment(s) Form

Optional Components:
PHS398 Cover Letter File

Foreign Organizations (Non-domestic (non-U.S.) Entity)
Applications from foreign organizations must:

- Request budgets in U.S. dollars.
- Prepare detailed budgets for all applications (that is, complete the Research & Related Budget component of the SF424).
- Not seek charge back of customs and import fees.
- Make every effort to comply with the format specifications, which are based upon a standard U.S. paper size of 8.5 x 11 within each PDF.
- Comply with Federal/FDA policies on human subjects, animals, and biohazards.
- Comply with Federal/FDA biosafety and biosecurity regulations. See Section VI.2., Administrative and National Policy Requirements.
- Indicate in the 398 Research Plan 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.

Proposed research should provide special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions in other countries that are not readily available in the United States or that augment existing U.S. resources.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Page limitations of the PHS398 Research Plan component must be followed as outlined in the SF424 (R&R) Application Guide unless otherwise stated per FDA's guidelines located at http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm186346.htm. Although each section of the Research Plan component needs to be uploaded separately as a PDF attachment, applicants are encouraged to construct the Research Plan component as a single document, separating sections into distinct PDF attachments just before uploading the files. This approach will enable applicants to better monitor formatting requirements such as page limits. All attachments must be provided to FDA in PDF format, filenames must be included with no spaces or special characters, and a .pdf extension must be used.

Resource Sharing Plan: Not Applicable.

Appendix: Do not use the Appendix to circumvent page limits of the Research Plan component. An application that does not observe the required page limitations may be delayed in the review process. Applicants **must** follow the specific instructions on Appendix materials as described in the SF424 (R&R) Application Guide (See http://grants.nih.gov/grants/funding/424/index.htm).

Foreign Institutions

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.

3. Submission Dates and Times

Part I. Overview Information contains information about Key Dates. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections

that might be necessary for successful submission.

Organizations must submit applications to Grants.gov (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons, FDA's electronic system for grants administration. Grants.gov and eRA Commons systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date. If a Changed/Corrected application is submitted after the deadline, the application will be considered late.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

See Section IV.3.A. for details.

Submission, Review, and Anticipated Start Dates

Opening Date: December 4, 2014 (Earliest date an application may be submitted to Grants.gov)
Letters of Intent Receipt Date(s): Not Applicable.
Application Due Date(s): February 4, 2015; February 3, 2016; February 1, 2017; February 7, 2018
Resubmission Due Date(s): October 15, 2015; October 14, 2016; October 16, 2017; October 15, 2018
Objective Review Date(s): May 2015, 2016, 2017, 2018 and November 2015, 2016, 2017, 2018
Council Review Date(s): September 2015, 2016, 2017, 2018 and February 2016, 2017, 2018, 2019
Earliest Anticipated Start Date(s): November 2015, November 2016, November 2017, November 2018

Please note that there is only one receipt date for FY 2016, one receipt date for FY 2017, one receipt date for FY 2018, and one receipt date for FY 2019 for new and resubmitted applications. Resubmissions and applications that were submitted previously will be allowed to resubmit October 15, 2015, October 14, 2016, October 16, 2017, and October 15, 2018. Resubmissions will also be accepted in the February receipt dates in both Fiscal years.

NOTE: An on-time submission means that an application is successfully submitted to Grants.gov no later than 11:59 p.m. eastern time on the application due date. The FDA Policy on late Submission of Grant Applications is: The applicant must seek a waiver no later than 5 days prior to the application deadline with explanation. The waiver request must be sent via e-mail to the Chief Grants Management Officer, Kimberly Pendleton Chew, at Kimberly.pendleton@fda.hhs.gov with a cc to the listed grant management specialist. Subject Line should include "Late Submission Waiver Request" and the Institution's and Principal Investigator's Name. Please Note: This does not guarantee application acceptance.

The protocol in the grant application should be submitted to the IND/IDE no later than January 5, 2015 for FY 2016, no later than January 4, 2016 for FY 2017, no later than January 2, 2017 for FY 2018, and no later than January 8, 2018 for FY 2019. **The current version of the protocol that is included in the grant application and is intended to be used if the study is funded is the protocol that MUST be submitted to the IND/IDE before the application is reviewed. The date that corresponds with the IND/IDE submission/amendment date that corresponds to the protocol in the grant application should be reported in the title of the grant with the IND/IDE number. For resubmissions, if any changes to the protocol have occurred since the last review due changes you are proposing, the protocol must be resubmitted as an amendment to the IND/IDE prior to the October resubmission dates and that date the protocol was submitted to the IND/IDE should be included in the title of the grant on the SF424(R&R) Form.**

Submitting an Application Electronically to the FDA

To submit an application in response to this FOA, applicants should access this FOA via http://www.grants.gov/applicants/apply_for_grants.jsp and follow Steps 1-4. Note: Applications must only be submitted electronically. **PAPER APPLICATIONS WILL NOT BE ACCEPTED.**

In order to expedite the review, applicants are requested to notify the FDA Referral Office by email vieda.hubbard@fda.hhs.gov when the application has been submitted. Please include the FOA number and title, PD/PI name, and title of the application.

Application Processing

Applications **may** be submitted on or after the opening date and **must** be successfully received by Grants.gov no later than **11:59 p.m. eastern time** on the application due date(s). 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. (See Section IV.3.A.for all dates.) If an application is not submitted by the due date(s) and time, the application may be delayed in the review process or not reviewed.

Once an application package has been successfully submitted through Grants.gov, any errors have been addressed, and the assembled application has been created in the eRA Commons, the PD/PI and the Authorized Organization Representative/Signing Official (AOR/SO) have two weekdays (Monday-Friday, excluding Federal holidays) to view the application image to determine if any further action is necessary.

- If everything is acceptable, no further action is necessary. The application will automatically move forward for processing after two business days, excluding Federal holidays.
- Prior to the submission deadline, the AOR/SO can Reject the assembled application and submit a changed/corrected application within the two day viewing window. This option should be used if it is determined that some part of the application was lost or did not transfer correctly during the submission process, the AOR/SO will have the option to Reject the application and submit a Changed/Corrected application. In these cases, please contact the eRA Help Desk to ensure that the issues are addressed and corrected. Once rejected, applicants should follow the instructions for correcting errors in Section 2.12 of the SF424 (R&R) Application Guide (http://grants.nih.gov/grants/funding/424/index.htm#), including the requirement for cover letters on late applications. The Reject feature should also be used if you determine that warnings are applicable to your application and need to be addressed now. **Remember, warnings do not stop further application processing.** If an application submission results in warnings (but no errors), it will automatically move forward after two weekdays if no action is taken. Some warnings may need to be addressed later in the process. If the two day window falls after the submission deadline, the AOR/SO will have the option to Reject the application if, due to an eRA Commons or Grants.gov system issue, the application does not correctly reflect the submitted application package (e.g., some part of the application was lost or didn't transfer correctly during the submission process). The AOR/SO should first contact the eRA Commons Helpdesk (http://ithelpdesk.nih.gov/eRA/) to confirm the system error, document the issue, and determine the best course of action. FDA will not penalize the applicant for an eRA Commons or Grants.gov system issue with an eRA Commons Helpdesk ticket number.
- If the AOR/SO chooses to Reject the image after the submission deadline for a reason other than an eRA Commons or Grants.gov system failure, a changed/corrected application still can be submitted but it will be subject to the NIH/FDA late policy (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-030.html) guidelines and may not be accepted. The reason for this delay should be explained in the cover letter attachment. Late applications may be accepted under extreme circumstances beyond the control of the applicant. In the absence of such extreme circumstances beyond the applicant's control, applications not received on time will not be considered for review and will generally be returned to the applicant.
- Both the AOR/SO and PD/PI will receive e-mail notifications when the application is rejected or the application automatically moves forward in the process after two days.
- In unusual circumstances, additional information may be considered, on a case by case basis, for inclusion in the objective expert panel review, however, the FDA cannot assure inclusion of any information after the receipt date other than evidence of final IRB approval, FWA or assurance, and certification of adequate supply of study product.

Upon receipt, applications will be evaluated for completeness. Incomplete applications will not be reviewed.

There will be an acknowledgement of receipt of applications from Grants.gov and the Commons. The submitting AOR receives the Grants.gov acknowledgments. The AOR and the PI receive Commons acknowledgments. Information related to the assignment of an application to a Scientific Review Group is also in the Commons.

Note: Since email can be unreliable, it is the responsibility of the applicant to check periodically on their application status in the Commons.

FDA will not accept any application in response to this FOA that is essentially the same as one currently pending initial merit review unless the applicant withdraws the pending application. FDA will not accept any application that is essentially the same as one already reviewed. However, the FDA will accept a resubmission application, but such application must include an Introduction (1 page maximum) addressing the critique from the previous review.

4. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All FDA awards are subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement.

Protection of Human Research Subjects

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 at http://www.hhs.gov/ohrp 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 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

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. 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. All human subject research regulated by FDA is also subject to FDA's regulations regarding the protection of human subjects (21 CFR parts 50 and 56). Applicants are encouraged to

review the regulations, guidance, and information sheets on human subject protection and good clinical practice available on the Internet at http://www.fda.gov/oc/gcp/.

Key Personnel and Human Subject Protection Education

The awardee institution is responsible for ensuring that all key personnel receive appropriate training in their human subject protection responsibilities. Key personnel include all principal investigators, co-investigators, and performance site investigators responsible for the design and conduct of the study. HHS, FDA, and OPD do not prescribe or endorse any specific education programs. Many institutions have already developed educational programs 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/ and by OHRP at http://www.hhs.gov/ohrp/education/.

Within 30 days of the award, the principal investigator should provide a letter to FDA's grants management office that includes the names of the key personnel, the title of the human subjects protection education program completed for each key personnel, and a one-sentence description of the program. This letter should be signed by the principal investigator and cosigned by an institution official and sent to the Grants Management Specialist whose name appears on the official Notice of Grant Award (NGA).

6. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. PAPER APPLICATIONS WILL NOT BE ACCEPTED.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically.

> **Important reminders:**
> All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to FDA. See Section III of this FOA for information on registration requirements.
>
> The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.
>
> See more tips for avoiding common errors.

Upon receipt, applications will be evaluated for completeness. Applications that are incomplete will not be reviewed.

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 consent forms should be attached in an appendix section. The applicant is referred to HHS and FDA regulations at 45 CFR 46.116 and 21 CFR 50.25 for details regarding the required elements of informed consent.

PD/PI Credential (e.g., Agency Login)

FDA requires the PD/PI(s) to fill in his/her Commons User ID in the PROFILE Project Director/Principal Investigator section, Credential log-in field of the Research & Related Senior/Key Person Profile component.

Organizational DUNS

The applicant organization must include its DUNS number in its Organization Profile in the eRA Commons. This DUNS number must match the DUNS number provided at System for Award Management (SAM) (formerly CCR) registration with Grants.gov. For additional information, see Frequently Asked Questions Application Guide, Electronic Submission of Grant Applications.

Section V. Application Review Information

1. Criteria

General Information

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 the requirements of this notice. Applications found to be non-responsive will receive notice that the application will not be reviewed.

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 Agency Contacts in Section VII of this document).

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 may be subject to a second review by the National Cancer Institute, National Cancer Advisory Board (NCAB) 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. **By submitting an application in response to this RFA, applicants understand and agree that members of the objective review panel of experts and the NCAB may be provided access to non-public information contained in the grant application, as necessary for evaluation of the application and subject to necessary restrictions on the further disclosure of the information.**

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 OPD grant program.

Applications submitted in response to this FOA will compete for available funds with all other recommended applications submitted in response to this FOA. The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by objective review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

The goal of FDA's OPD grant program is to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the product will be superior to the existing therapy. In their written critiques, reviewers will be asked to comment on each of the following criteria in addition to the Scientific/Technical Review Criteria outlined below, in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these

goals. Each of these criteria will be addressed and considered in assigning the overall score, and weighted as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a meritorious priority score.

Investigators: Assessing the competence of the principal investigator(s) and key personnel to conduct the proposed research. This includes their academic qualifications, research experiences, productivity, and any special attributes.

Resources and Environment: Evaluating any special attributes or deficiencies relevant to the conduct of the proposed studies.

Budget: Evaluating whether all items of the requested budget are appropriate and justified.

Human Subjects and Monitoring: Evaluating possible physical, psychological, or social injury patients might experience as subjects in the proposed research. Discussing whether the rights and welfare of the individuals will be adequately protected. Assessing the safety-monitoring plan including the reporting of adverse events. Evaluating the informed consent documents as well as the plan to monitor the integrity of the data collected and the compliance with the protocol.

Scored Review Criteria - Scientific/Technical Review Criteria

The objective review 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 the 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 and monitoring; and

8. The ability of the applicant to complete the proposed study within its budget and within time limits stated in this FOA.

Program Review Criteria

1. Applications must propose clinical trials intended to provide safety and/or efficacy data.

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 Background and Significance section of the application must contain information documenting that the disease or condition to be treated meets the definition of a rare disease or condition, as defined in 21 U.S.C. 360ee. FDA generally considers drugs, devices, and medical foods potentially eligible for grants under the OPD grant program if they are indicated for a disease or condition that

has a prevalence, not incidence, of fewer than 200,000 people in the United States. Diagnostics and vaccines are considered potentially eligible for such grants only if the U.S. population to whom they will be administered is fewer than 200,000 people in the United States per year. Prevalence calculations should be provided along with citations. If a designation by the Office of Orphan Products Development has been received by the institution submitting the grant for the drug for the disease subject to the grant, the designation number and date of designation should be provided in this section.

4. With the exception noted below, 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 applicable FDA IND/IDE review 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 in both the IND/IDE and in the grant application. The name(s) of the principal investigator(s) named in the application and in the study protocol must be 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 pre-market approval and medical devices that are classified as non-significant risk (NSR) are free from these IND/IDE requirements. Applicants studying an NSR device should provide a letter in the application from the FDA Center for Devices and Radiologic Health indicating the device is an NSR device.

5. The requested budget must be within the limits, either $250,000 in total costs per year for up to 3 years for any phase study, or $500,000 in total costs per year for up to 4 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 non-responsive.

6. In an appendix to the application, there must be evidence that the product to be studied is available to the applicant in the form and quantity needed for the clinical trial proposed. A current letter from the supplier as an appendix will be acceptable. If negotiations regarding the supply of the study product are underway but have not been finalized at the time of application, please provide a letter indicating such in the application. Verification of adequate supply of study product will be necessary before an award is made.

7. The protocol and the informed consent form should be submitted in the application. The protocol and the informed consent form may be included as an appendix. Page limits, font size and margins should comply with the Application Guide, Electronic Submission of Grant Applications (http://era.nih.gov/ElectronicReceipt/faq_prepare_app.htm#1).

8. Additional information may be required upon request, for example, regarding population estimate and rationale. This additional information may be required, in part, to assure that human clinical trials of drugs are eligible to receive funding under the OPD grant program. 21 U.S.C. 360ee(b)(1)(A).

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for

involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects. See the Human Subjects Sections of the PHS398 Research Plan component of the SF424 (R&R).

Inclusion of Women, Minorities, and Children

The committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children as appropriate to determine if it is justified in terms of the scientific goals and research strategy proposed. See the Human Subjects Sections of the PHS398 Research Plan component of the SF424 (R&R). For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project. The adequacy of the responses to comments from the most recent scientific review group will be assessed including the appropriateness of the improvements in the resubmission application.

Applicants may submit a resubmission application, but such application must include an Introduction addressing the previous objective review critique (Summary Statement). The Summary Statement issued from the Office of Orphan Products Development must be included as an Appendix in the resubmission application.

Resubmissions are intended for those applications that were previously submitted to OPD, reviewed and received a score on the application.

Renewals

Renewal applications will be permitted for this FOA. For Renewals, the committee will consider the progress made in the last funding period.

Revisions

Active grants in regulatory compliance may be eligible to submit a competing supplement application. A competing supplement (also called Revision) is a request for additional funds for a current award to expand the scope of work. Competing supplements may be submitted throughout the fiscal year and will be permitted for this FOA to compete for funding.

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Please contact the OPD program contact for further information.

Additional Review Considerations
As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations
Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Resource Sharing Plans
Not Applicable.

Budget and Period of Support
Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

2. Review and Selection Process
Applications will be evaluated for scientific and technical merit by appropriate Scientific Review Groups, using the stated review criteria.

Applications will compete for available funds with all other recommended applications submitted in response to this FOA. Following initial peer review, recommended applications will receive a second level of review by the appropriate national Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

3. Anticipated Announcement and Award Dates
After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons.

Earliest Anticipated Start/Award Date(s): November 1, 2015, November 1, 2016, November 1, 2017, and November 1, 2018

Section VI. Award Administration Information

1. Award Notices
If the application is under consideration for funding, FDA may request information from the applicant prior to making the award. For details, applicants may refer to the HHS Grants Policy Statement.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization. The NoA signed by the grants management officer is the authorizing document. Once all administrative and programmatic issues have been resolved, the NoA will be generated via email notification from the awarding component to the grantee business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

After the review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons.

2. Administrative and National Policy Requirements

All FDA grant and cooperative agreement awards include the HHS Grants Policy Statement as part of the NoA. For these terms of award, see the HHS Grants Policy Statement.

3. Reporting

When multiple years are involved, awardees will be required to submit the annual Non-Competing Progress Report (PHS 2590) annually and financial statements as required in the HHS Grants Policy Statement.

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the HHS Grants Policy Statement.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable FDA grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000.

Monitoring Activities

The guidelines below are intended to provide information for principal investigators who are conducting clinical trials. The procedures outlined herein are in addition to (and not in lieu of) Institutional Review Board (IRB), Office for Human Research Protections (OHRP), other Food and Drug Administration (FDA), and Good Clinical Practices requirements.

It is an OPD policy that data and safety monitoring of a clinical trial is to be commensurate with the risks posed to study participants and with the size and complexity of the study. In addition, the OPD requires that a Grantee and any third party engaged in supporting the clinical research be responsible for oversight of data and safety monitoring, ensuring that monitoring systems are in place, that the quality of the monitoring activity is appropriate, and that the OPD Project Officer is informed of recommendations emanating from monitoring activities.

FDA Requirements for Monitoring

The OPD requires that each clinical trial it supports, regardless of phase, has data and safety monitoring procedures in place to safeguard the well-being of study participants and to ensure scientific integrity. Monitoring must be performed on a regular basis throughout the subject accrual, treatment, and follow-up periods.

The specific approach to monitoring will depend on features of the clinical trial to be conducted e.g., several levels of monitoring: Data and Safety Monitoring Board (DSMB), Study Monitoring Committee (SMC) and Independent Medical Monitor (IMM). Monitoring activities should be appropriate to the study, study phase, population, research environment, and degree of risk involved. Guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf.

In small, single-site studies, safety monitoring is often performed by the independent medical monitor or a safety monitoring committee in conjunction with the study statistician. Phase 3 studies and high risk Phase 1 or 2 clinical trials frequently use a DSMB. It may be desirable to utilize a DSMB for:

- Trials involving highly experimental therapies or specialized review procedures external to the OPD (e.g., gene therapy or xenotransplantation);
- Trials involving substantial risk to study participants (e.g., studies with irreversible outcomes); or
- Trials involving particularly vulnerable study participants (e.g., children or persons with impaired ability to consent).

Study Monitoring Plan

The OPD requires that the protocol document include a section describing the proposed plan for interim data monitoring. This section will detail who is to be responsible for interim monitoring (i.e., a DSMB, an SMC, or the study investigator), what data will be monitored (i.e., performance and safety data only vs. efficacy data as well), the timing of the first data review (e.g., "the first interim look will occur when the initial 20 participants have completed the 6 month follow-up visit"), and the frequency of interim reviews (which will depend on such factors as the study design, interventions and anticipated recruitment rate). The plan will specify "stopping guidelines" and other criteria for the monitors to follow in their review of the interim data. Guidance on these topics is available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf.

A preliminary monitoring plan must be submitted as part of the Research Plan portion of the grant application for a clinical trial. The plan will be examined as part of the objective review process, and any comments and concerns will be included in an administrative note in the summary statement. OPD staff will ensure that all concerns are resolved before the grant award is made.

Oversight Activities

The program project officer will monitor grantees periodically. The monitoring may be in the form of telephone conversations, e-mails, or written correspondence between the project officer/grants management officer or specialist and the principal investigator. Information including, but not limited to, information regarding study progress, enrollment, problems, adverse events, changes in protocol, and study monitoring activities will be requested. Periodic site visits with officials of the grantee organization may also occur. The results of these monitoring activities will be recorded in the official grant file and will be available to the grantee upon request consistent with applicable disclosure statutes and with FDA disclosure regulations. Also, the grantee organization must comply with all special terms and conditions of the grant, including those which state that future funding of the study will depend on recommendations from the OPD project officer. The scope of the recommendations will consider the following: (1) progress toward enrollment, based on specific circumstances of the study; (2) adequate supply of the product/device; and (3) compliance with applicable FDA and HHS regulatory requirements for the trial.

In addition to the requirement for an active IND/IDE discussed in Section V.3 of this document, documentation of assurances with the Office of Human Research Protection (OHRP) (see Section IV.5.A of this document) must be on file with the FDA grants management office before an award is made. Any institution receiving Federal funds must have an institutional review board (IRB) of record even if that institution is overseeing research conducted at other performance sites. To avoid funding studies that may not receive or may experience a delay in receiving IRB approval, documentation of IRB approval and Federal Wide Assurance (FWA or assurance) for the IRB of record for all performance sites must be on file with the FDA grants management office before an award to fund the study will be made. In addition, if a grant is awarded, grantees will be informed of any additional documentation that should be submitted to FDA's IRB.

Reporting Requirement

The grantee must file a final program progress report, financial status report, and invention statement within 90 days after the end date of the project period as noted on the notice of grant award.

When multiple years are involved, awardees will be required to submit the Non-Competing Grant Progress Report (PHS 2590) annually and financial statements as required in the HHS Grants Policy Statement, dated January 1, 2007 (http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf). Also, all new and continuing grants must comply with all regulatory requirements necessary to keep the status of their IND/IDE active and in effect, that is, not on clinical hold. Failure to meet regulatory requirements will be grounds for suspension or termination of the grant.

Awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually and financial statements as required in the HHS Grants Policy Statement http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf.

A listing and a justification for any study changes that occurred in the past year must be included in the Non-Competing Continuation Grant Progress Report (PHS 2590).

A final progress report, invention statement, and Financial Status Report are required when an award is relinquished when a recipient changes institutions or when an award is terminated.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

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

Grants.gov Customer Support (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact CenterTelephone: 800-518-4726
Web ticketing system: https://grants-portal.psc.gov/ContactUs.aspx
Email: support@grants.gov

Vieda Hubbard
Grants Management Specialist
Division of Acquisition Support and Grants
Office of Acquisitions & Grant Services
5630 Fishers Lane
Rockville, Maryland 20857
Phone: 240-402-7588
E-mail: vieda.hubbard@fda.hhs.gov

Scientific/Research Contact(s)

Katherine Needleman
Director, Orphan Products Grants Program
Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5295
Silver Spring, MD 20993-0002
Phone: 301-796-8660
E-mail: katherine.needleman@fda.hhs.gov

Financial/Grants Management Contact(s)

Vieda Hubbard
Grants Management Specialist
Division of Acquisition Support and Grants
Office of Acquisitions & Grant Services
5630 Fishers Lane
Rockville, Maryland 20857
Phone: 240-402-7588
E-mail: vieda.hubbard@fda.hhs.gov

Section VIII. Other Information

1. Required Federal Citations

Clinical Trials Data Bank

The Food and Drug Administration Amendments Act of 2007 (FDAAA) contains provisions that expand the current database known as ClinicalTrials.gov to include additional requirements for individuals and entities, including grantees, who are involved in conducting clinical trials that involve products regulated by FDA or that are funded by the Department of Health and Human Services (HHS), including FDA. These additional requirements include mandatory registration of certain types of clinical trials, as well as reporting of results for certain trials for inclusion in the ClinicalTrials.gov database. ClinicalTrials.gov, which was created after the Food and Drug Administration Modernization Act of 1997, provides patients, family members, healthcare providers, researchers, and members of the public easy access to information on clinical trials for a wide range of diseases and conditions. The U.S. National Library of Medicine (NLM) has developed this site in collaboration with NIH and FDA. ClinicalTrials.gov is available to the public through the Internet at http://clinicaltrials.gov.

ClinicalTrials.gov contains information about certain clinical trials, both federally and privately funded, of drugs (including biological products) and medical devices. The types of trials that are required to be registered, and for which results must be reported, are known as "applicable clinical trials." FDAAA defines the types of clinical trials that are "applicable clinical trials" and, therefore, are subject to the registration and results reporting requirements. The registry listing for each trial includes information such as descriptive information about the trial, patient eligibility criteria, recruitment status, location information on the clinical trial sites, and points of contact for those wanting to enroll in the trial. The database also contains information on the results of clinical trials. More detailed information on the definition of "applicable clinical trial" and the registry and results reporting requirements can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html and http://prsinfo.clinicaltrials.gov/fdaaa.html.

FDAAA also added new requirements concerning clinical trials supported by grants from HHS, including FDA. Under these provisions, any grant or progress report forms required under a grant from any part of HHS, including FDA, must include a certification that the person responsible for entering information into ClinicalTrials.gov (the "responsible party") has submitted all required information to the database. There are also provisions regarding when agencies within HHS, including FDA, are required to verify compliance with the database requirements before releasing funding to grantees. OPD program staff will be providing additional information on these requirements, including the appropriate means by which to certify that a grantee has complied with the database requirements.

Data and Safety Monitoring Plan

See Section VI.3.A. for more detail and other FDA monitoring requirements. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase 3 clinical trials.

Although Phase 1 and Phase 2 clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

Access to Research Data through the Freedom of Information Act (FOIA)

The Freedom of Information Act (FOIA), 5 U.S.C. 552, provides individuals with a right to access certain records in the possession of the Federal government, subject to certain exemptions. The government may withhold information pursuant to the exemptions and exclusions contained in the FOIA. The exact language of the exemptions can be found in the FOIA. Additional guidance on the exemptions and how they apply to certain documents can be found in the HHS regulations implementing the FOIA (45 CFR part 5) and FDA regulations implementing the FOIA (21 CFR part 20). (Also see the HHS Web site http://www.hhs.gov/foia/ and FDA Web site at http://www.fda.gov/RegulatoryInformation/FOI/default.htm)

Data included in the application may be considered trade secret or confidential commercial information within the meaning of relevant statutes and implementing regulations. FDA will protect trade secret or confidential commercial information to the extent allowed under applicable law.

Use of Animals in Research

Recipients of PHS support for activities involving live vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://awic.nal.usda.gov/nal_display/index.php?info_center=3&tax_level=3&tax_subject=182&topic_id=1118&level3_id=6735&level4_id=0&level5_id=0&placement_default=0) as applicable.

Inclusion of Women And Minorities in Clinical Research

Applicants for PHS clinical research grants are encouraged to include minorities and women in study populations so research findings can be of benefit to all people at risk of the disease or condition under study. It is recommended that applicants place special emphasis on including minorities and women in studies of diseases, disorders, and conditions that disproportionately affect them. This policy applies to research subjects of all ages. If women or minorities are excluded or poorly represented in clinical research, the applicant should provide a clear and compelling rationale that shows inclusion is inappropriate.

Inclusion of Children as Participants in Clinical Research

FDA regulations at 21 CFR part 50, subpart D contain additional requirements that must be met by IRBs reviewing clinical investigations regulated by FDA and involving children as subjects. FDA is part of HHS; accordingly, the research project grants under this program are supported by HHS, and HHS regulations at 45 CFR part 46, subpart D also apply to research involving children as subjects.

Standards for Privacy of Individually Identifiable Health Information

HHS issued final modification to the Standards for Privacy of Individually Identifiable Health Information, the Privacy Rule, on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the HHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR Web site http://www.hhs.gov/ocr/ provides information on the Privacy Rule.

Healthy People 2020

PHS is committed to achieving the health promotion and disease prevention objectives of Healthy People 2020, a PHS-led national activity for setting priority areas. This Funding Opportunity Announcement is related to one or more of the priority areas. Potential applicants may obtain a copy of Healthy People 2020.

Smoke-Free Workplace

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Authority and Regulation

This program is not subject to the intergovernmental review requirements of Executive Order 12372. FDA's research program is described in the Catalog of Federal Domestic Assistance (CFDA), No. 93.103 http://www.cfda.gov/.

FDA will support the clinical studies covered by this notice under the authority of section 301 of the PHS Act as amended (42 U.S.C. 241) and under applicable regulations at 42 CFR Part 52 and 45 CFR Parts 74 and 92. All grant awards are subject to applicable requirements for clinical investigations imposed by sections 505, 512, and 515 of the act (21 U.S.C. 355, or 360e) or safety, purity, and potency for licensing under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), section 351 of the PHS Act, including regulations issued under any of these sections.

All human subject research regulated by FDA is also subject to FDA's regulations regarding the protection of human subjects (21 CFR Parts 50 and 56). Applicants are encouraged to review the regulations, guidance, and information sheets on human subject protection and Good Clinical Practice available on the Internet at http://www.fda.gov/oc/gcp/.

The applicant is referred to HHS regulations at 45 CFR 46.116 and 21 CFR 50.25 for details regarding the required elements of informed consent.

All awards will be subject to all policies and requirements that govern the research grant programs of the PHS as incorporated in the HHS Grants Policy Statement, dated January 1, 2007.