Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	U.S. Food and Drug Administration (FDA) The policies, guidelines, terms, and conditions stated in this announcement may differ from those used by the NIH. Where this Funding Opportunity Announcement (FOA) provides specific written guidance that may differ from the general guidance provided in the grant application form, please follow the instructions given in this FOA. 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 Objective Review Process.
Components of Participating Organizations	Center for Biologics Evaluation and Research (CBER)
Funding Opportunity Title	**Collaboration in Regulatory Systems Strengthening and Standardization Activities to Increase Access to Safe and Effective Biological Products - (U01)**
Activity Code	U01 Research Project – Cooperative Agreements
Announcement Type	New
Related Notices	None
Funding Opportunity Announcement (FOA) Number	**RFA-FD-16-044**
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 Food and Drug Administration (FDA) announces its intention to accept and consider a single source application for award to the World Health Organization (WHO) in support of collaboration in regulatory systems strengthening, development of norms and standards, and innovative research to advance global access to safe and effective biological products that meet international standards.

Key Dates

Posted Date	
Open Date (Earliest Submission Date)	May 5, 2016
Letter of Intent Due Date(s)	Not Applicable
Application Due Date(s)	July 5, 2016, by 11:59 PM Eastern Time. The applicant is 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. The applicant 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. **A late application will not be accepted for this FOA.**
AIDS Application Due Date(s)	Not Applicable

Scientific Merit Review	August, 2016
Advisory Council Review	Not Applicable
Earliest Start Date	September, 2016
Expiration Date	July 6, 2016
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 (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts*). 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.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

A. BACKGROUND:

The World Health Organization (WHO) is the directing and coordinating authority on international health within the United Nations' system. WHO coordinates international efforts to produce health guidelines and standards, and helps countries to address public health issues. WHO also promotes and supports research on matters related to health. WHO fulfils its global public health objectives through its core functions:

- Providing leadership and engaging in partnerships where joint action is needed;
- Setting norms and standards and promoting their implementation;
- Contributing to development of a research agenda and serving as a conduit for dissemination of information;
- Articulating ethical and evidence-based policy options;
- Providing technical support and building sustainable institutional capacity; and
- Monitoring the health situation in countries and regions and assessing health trends and needs.

WHO assists countries to increase and sustain access to medical products to prevent, detect, and treat communicable diseases, including reducing vaccine-preventable diseases. The WHO also coordinates response to public health emergencies by monitoring the health situation, undertaking risk assessments, identifying priorities, and providing technical guidance and other forms of support to countries and regions.

Providing regulatory oversight throughout the product life cycle (pre- and post-licensure) is a major challenge for many National Regulatory Authorities confronted by a steadily increasing number of novel products, complex quality concerns, new regulatory issues arising from rapid technical and technological advances, and emerging infectious diseases (e.g., pandemic influenza, MERS, Ebola, Zika). The WHO has an important role in strengthening regulatory systems and other supportive activities to increase access to high quality, safe, and effective biological products especially in low-and-middle-income countries.

The U.S. FDA's Center for Biologics Evaluation and Research (FDA/CBER) has been a leader and active participant in the global community to improve human health in the world's populations over many years. FDA, through CBER, has longstanding collaborations with the WHO in the area of biologicals (vaccines, blood and blood products, relevant *in vitro* diagnostics, and cell and tissue therapies). FDA/CBER has been a Pan American Health Organization (PAHO)/WHO Collaborating Center for Biological Standardization since 1998 with the current commitment running until February 2020 and expectation of future extensions. The purpose, scope and areas of activity for each term are captured in a set of "Terms of Reference" (TOR) mutually agreed to by FDA/CBER and PAHO/WHO, and are reflective of their shared interest in supporting development and global access to high quality, safe and effective biological products.

Development of Norms and Standards:

The World Health Organization (WHO) has played a key role for over 50 years in establishing WHO International Biological Reference Preparations and in developing WHO guidelines and recommendations on the production and control of vaccines and other biological products and technologies. The WHO Expert Committee on Biological Standardization (ECBS) is commissioned by WHO to advise the Organization on international standards setting activities.

Blood products are inherently variable due to the nature of the source materials as well as the methods used to test them. The objective is to ensure that only blood products of acceptable quality, safety and efficacy are used in the patient population. The WHO provides technical guidance and assistance to strengthen National Regulatory Authorities (NRAs) to assure the control and safety of blood products, and supports development and implementation of new manufacturing technologies to prevent transmission of blood-borne viral diseases via blood products.

Similarly, ensuring the quality, safety, and effectiveness of vaccines is one of WHO's highest priorities. The Global Vaccine Action Plan (GVAP), which was endorsed by the 194 Member States of the World

Health Assembly in May 2012, aims to strengthen routine immunization to meet vaccination coverage targets; accelerate control of vaccine-preventable diseases with polio eradication as the first milestone; and introduce new and improved vaccines and promote research and development for the next generation of vaccines and technologies. The WHO works in close collaboration with national authorities to ensure that global standards are developed and made readily available to assess the quality, safety and immunogenicity of vaccines, and to support monitoring vaccine safety throughout the product life cycle.

Written guidelines and recommendations describe procedures for the manufacture and quality control testing of biological products to ensure that the products manufactured for human use conform to current international standards. Regulatory guidance documents advise NRAs and manufacturers on the control of biological products, and aim to establish regulatory convergence or harmonization for products that have a global market. Through guidelines and other written international standards, NRAs can maintain current knowledge on the scientific background needed to assess critical issues, and have access to advice on which regulatory approaches and methodologies are optimal for ensuring the global supply of uniformly high quality and efficacious biological products.

International reference materials are essential for standardization and comparison of biological measurements worldwide. Well-characterized preparations are needed as global measurement standards against which batches of biological products are assessed. This is fundamental to ensuring the quality of biological products, the consistency of production of these products, and appropriate clinical dosing. WHO International Biological Reference Preparations serve as reference sources for defining and expressing biological activity in agreed upon international units.

WHO international standards are developed based on scientific consensus achieved through global consultations, and implementation of these standards assists WHO Member States to ensure the quality, safety, and effectiveness of biological products and related *in vitro* diagnostic tests worldwide.

Regulatory Systems Strengthening:

In this era of globalization, products can be imported from anywhere in the world making supply chains for biological products increasingly complex. The establishment of strong regulatory systems is very important for FDA's ability to fulfill its mission to better monitor and ensure the safety of the supply chain for medical and other products entering the United States from other parts of the world.

National Regulatory Authorities play a vital role in the national health care system. In 2014, the sixty-seventh World Health Assembly passed resolution WHA67.20 ("Regulatory System Strengthening for Medical Products") emphasizing WHO's role in strengthening regulatory systems for medical products, and in supporting NRAs and relevant regional and international networks that support regulatory activities. The resolution mandates WHO to support Member States in: (i) evaluating national regulatory systems (using WHO's harmonized NRA assessment tool); (ii) generating and analyzing evidence of regulatory system performance; (iii) facilitating the formulation and implementation of institutional development plans to fill gaps and; (iv) providing technical support to National Regulatory Authorities and governments to address deficiencies and enhance capacity.

A robust regulatory system for medical products must include a legal framework, and the mandate to carry out and enforce critical functions including: marketing authorization (licensing); oversight of good manufacturing, pre-clinical, and clinical practices; monitoring and evaluating product quality (laboratory function); lot release; inspections (GMP compliance); monitoring safety and vigilance (surveillance capacity) throughout product life cycle; and capacity to respond to emergency situations (perform risk assessment, analysis, and manage response). Resolution WHA67.20 gives WHO the mandate to promote and support regulatory system strengthening as an integrated part of health system development.

WHO Prequalification Program:

The WHO Prequalification Program was established in response to the need to supply quality health products, including vaccines and *in vitro* diagnostic tests for the prevention, diagnosis and treatment of priority diseases in low-and-middle-income countries. Through the prequalification program, WHO

assures the quality, safety and efficacy/performance of these products, and suitability for use in the target settings.

For the Vaccine Prequalification Program, WHO provides advice to the United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies on the acceptability, in principle, of vaccines considered for purchase by such agencies for vaccination programs they administer. An important part of the Vaccine Prequalification Program is WHO's reliance upon a competent National Regulatory Authority to provide regulatory oversight for the vaccine throughout the life cycle. In 2009, FDA entered into a confidentiality arrangement with WHO to enable FDA/CBER to serve as an NRA of record under this prequalification program, and the Center is currently an NRA of record for nine U.S. licensed vaccines.

Product Safety and Vigilance:

The safety of medical products depends on a variety of factors that range from good manufacturing practices to strong national systems able to monitor the products in domestic markets. However, with increasing globalization of trade, overall effective surveillance of medical products depends on international regulatory cooperation and information sharing. WHO promotes the global safety of medical products by coordinating global networks for information sharing, such as data bases and monitoring and alert systems, and by supporting countries to develop national capacities for the post-marketing surveillance of health products. About two thirds of countries do not have a functional post-marketing surveillance system to monitor vaccine adverse events. To address this issue, WHO and partners have developed a strategic framework ("Global Vaccine Safety Blueprint") to promote the establishment of effective vaccine pharmacovigilance systems in all countries by 2020. The Blueprint proposes a strategic plan for strengthening vaccine safety activities globally, focusing on building national capacity for vaccine safety in the world's poorest countries through the coordinated efforts of major stakeholders.

Additionally, WHO advisory bodies play a significant role in monitoring product safety and vigilance. The Global Advisory Committee on Vaccine Safety (GACVS) provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern. The GACVS rigorously reviews the latest knowledge concerning any aspect of vaccine safety of global or regional interest, determines causal relationships between vaccines and/or their components and adverse events attributed to them, and provides scientific recommendations to assist WHO, the WHO's Strategic Advisory Group of Experts (SAGE) for vaccines and immunization, national governments and international organizations in formulating policies regarding vaccine safety issues.

Similarly, the Blood Regulators' Network (BRN) serves as an advisory body to WHO on matters related to safety and availability of blood and blood products. The BRN provides a forum for the exchange of information and opinion among regulators on blood-related issues. The BRN focuses on scientific assessment of current and emerging threats to the safety and availability of blood and blood products, assessment of the impact of new blood-related technologies, and also explores opportunities for regulatory cooperation and collaboration, where possible.

Regulatory science to promote development and increased access to safe and effective biological products:

Regulatory oversight is critical for ensuring that biological products used in humans are safe, effective, and of assured quality. Regulatory science aims to contribute to the development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated biological products. Examples include tools to standardize assays used for regulatory purposes (e.g., development of correlates of immunity; correlates of safety; improved methods for product characterization; new or alternative potency assays etc.). Results generated through methods and tools developed through regulatory science efforts such as adaptive clinical trial designs, benefit/risk assessment, novel pharmacovigilance methodologies, and other tools inform regulatory decision-making processes. Knowledge gained through regulatory science can play a significant role in CBER's regulatory decision-making, policy development, and preparedness to address threats from existing or emerging infectious diseases. The challenges of modern product development and globalization

underscore the critical importance of modernizing and advancing regulatory science to match advances in basic and applied science and technology.

B. RESEARCH OBJECTIVES:

The FDA, with other HHS technical agencies and offices, the WHO, and other regulatory counterparts, are strategizing on approaches to increase access of the global population to safe and effective biological products for the prevention, diagnosis, and treatment of priority diseases, especially for use in low-and-middle-income countries.

This project represents a collaborative effort between FDA and the WHO (and complements and builds upon the US Government's existing commitments with WHO) to support scientific collaboration and enhance regulatory capabilities of National Regulatory Authorities and networks to advance global access to safe and effective vaccines and other biologicals that meet international standards. This project will further support science-based and data-driven public health strategies and approaches, and lead to improved technical cooperation between FDA, WHO, and its Member States.

The project has the following goals:

1. Contribute to the knowledge base of the current state of regulatory oversight of vaccines and biological products
- Support NRA assessments and analyses and synthesis of the data, and development of an Institutional Development Plan to enhance regulatory performance in low-and-middle-income countries. Assessment of regulatory systems could include but is not limited to, analyses and synthesis of existing data from assessments of vaccine regulatory capabilities of different NRAs, and new applications of assessment frameworks to specific areas, such as pharmacovigilance (e.g., monitoring safety and effectiveness of new vaccines following introduction in a specific country or regional setting). NRA assessments also support WHO's vaccine prequalification program;
- Analysis of regulatory systems performance can include assessment of challenges, risks, and emerging trends, with the aim of further strengthening the development of data/information systems as sources of inputs for evidence-based regulatory decisions and actions;
- Expected outputs could include analyses, reports and data-driven strategy papers, among others.

2. Providing technical support to regulatory systems strengthening efforts
- Enable the strengthening of regulatory systems at the national and regional levels in such critical domains as good manufacturing, clinical, and laboratory practices; monitoring and evaluation of product quality; lot release; inspection and surveillance of products throughout the supply chain; pharmacovigilance systems building and analyses; risk assessment, analysis, and management etc.;
- Support the diffusion and application of knowledge, data and information through active participation in regional and global committees and networks, such as the African Vaccine Regulatory Forum (AVAREF), Expert Committee on Biological Standardization (ECBS), Global Advisory Committee on Vaccine Safety (GACVS), Blood Regulators' Network (BRN), etc.
- Expected outputs could include analyses, reports and data-driven strategy papers, among others.

3. Development of global norms and standards
- Enable the timely and effective sharing of scientific findings and data through international collaboration to develop WHO International Biological Reference Preparations and WHO guidelines and recommendations on the production and control of vaccines and other biological products and technologies;
- Assist Member States in the implementation of internationally-recognized standards and guidelines, e.g. WHO guidelines and standards and those emerging from standards development venues such as the International Council for Harmonisation of the Technical Requirements for Pharmaceuticals for Human Use (ICH);
- Utilize WHO's convening power to engage with relevant stakeholders in support of data-driven and science-based public health strategies and approaches to enhancing global regulatory capacity and cooperation;

- Expected outputs could include guideline documents, physical standards (e.g., reference reagents, reference panels etc.), reports and data-driven strategy papers, among others.

4. Supporting regulatory science and other activities to promote development and increased access to safe and effective biological products
- Enable development of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated biological products;
- Support programs, including but not limited to WHO prequalification, that increase access to safe and effective biological products;
- Expected outputs could include analyses, reports and data-driven strategy papers, among others.

Inherent in the cooperative agreement award is substantive involvement by the awarding agency. Accordingly, FDA/CBER will have substantive involvement in the programmatic activities funded by this Cooperative Agreement. Substantive involvement includes, but is not limited, to the following:

1. FDA will appoint a project officer or co-project officers who will actively monitor the FDA-supported program under this award. FDA's CBER will serve as the Technical Lead for FDA's involvement.

2. FDA will provide guidance, direction, and assistance in design and development of the approaches and methods that may be used by the recipient.

3. As appropriate to the implementation of this award, FDA will participate with WHO to determine the scope of: (a) opportunities for diffusion and application of knowledge and (b) development of reports and analyses, and (c) publication of articles and (d) media releases.

4. Working collaboratively with the WHO and its Member States, FDA will participate in scientific meetings; design of assessments, and review, analysis, and publication of assessment findings, where appropriate.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument	Cooperative Agreement: A support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, FDA scientific or program staff will assist, guide, coordinate, or participate in project activities. See Section VI.2 for additional information about the substantial involvement for this FOA
Application Types Allowed	New The OER Glossary and the SF424 (R&R) Application Guide provide details on these application types.
Funds Available and Anticipated Number of Awards	Award is contingent upon FDA appropriations and the submission of a sufficient meritorious application. Future year amounts will depend on annual appropriations, availability of funding and awardee performance. FDA/CBER intends to fund up to $2,000,000 for fiscal year 2016 in support of this grant program.

	It is anticipated that up to one (1) award will be made, not to exceed $2,000,000 in total costs (direct plus indirect), per award.
Award Budget	FDA/CBER anticipates providing in FY2016 up to $2,000,000 (total costs including indirect costs for one award subject to availability of funds) in support of this project. The application budget should reflect the actual needs of the proposed project and should not exceed the following in total costs (direct and indirect): YR 01: $2,000,000 YR 02: $2,000,000 YR 03: $2,000,000 YR 04: $2,000,000 YR 05: $2,000,000
Award Project Period	The scope of the proposed project should determine the project period. The maximum project period is five (5) years.

HHS 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

The following organization is eligible to apply:

- World Health Organization (WHO)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Foreign components, as defined in the HHS Grants Policy Statement, **are** allowed.

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.

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 FDA support.

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.

2. Cost Sharing

This FOA 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 duplicate or highly overlapping applications under review at the same time. This means that the FDA will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.

Section IV. Application and Submission Information

1. Requesting an Application Package

Applicants must obtain 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.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, including Supplemental Grant Application Instructions 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.

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.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R Budget

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

- Applications requesting multiple years of support must complete and submit a separate detailed

budget breakdown and narrative justification for each year of financial support requested.

- If an applicant is requesting indirect costs as part of their budget, a copy of the most recent Federal indirect cost rate or F&A agreement must be provided as part of the application submission. This agreement should be attached to the RESEARCH & RELATED Other Project Information Component as line #12 'Other Attachments'.

- If the applicant organization has never established an indirect cost rate and/or does not have a negotiated Federal indirect cost rate agreement, a de minimis indirect cost rate of 10 percent (10%) of modified total direct costs (MTDC) will be allowed. MTDC means all direct salaries and wages, applicable fringe benefits, materials and supplies, services, travel, and subaward and subcontracts up to the first $25,000 of each subaward or subcontract. MTDC excludes equipment, capital expenditures, charges for patient care, rental costs, tuition remission, scholarships and fellowships, participant support costs and the portion of each subaward and subcontract in excess of $25,000.

R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

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

- **Research Strategy:** The applicant must submit a Research Strategy with the application forms. The Research Strategy must be written according to the following outline (see Research Strategy Outline below).

- **Research Strategy Outline:**

1. Background/problem to be addressed
2. Goals/objectives
3. Milestones and timelines; include result/expected output if appropriate
4. Project Plan
5. Anticipated outcomes (include result/expected output where applicable)
6. Plan to monitor and evaluate progress; and
7. Dissemination/communication plan.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

- Generally, Resource Sharing Plans are expected, but they are not applicable for this FOA.

Appendix: Do not use the Appendix to circumvent page limits. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Inclusion Enrollment Report

When conducting clinical research, follow all instructions for completing PHS Inclusion Enrollment Report as described in the SF424 (R&R) Application Guide.

PHS Assignment Request Form

All instructions in the SF424 (R&R) Application Guide must be followed.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *HHS Grants Policy Statement*, and procedures for foreign institutions described throughout the SF424 (R&R) Application Guide.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. 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. eRA Commons and Grants.gov 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 and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. **Late applications will not be accepted for this FOA.**

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.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

6. Funding Restrictions

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

Pre-award costs are allowable only as described in the *HHS Grants Policy Statement*.

Additional funding restrictions may be part of the Notice of Award.

7. 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. For assistance with application submission, contact the

Application Submission Contacts in Section VII.

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 and compliance with application instructions by the assigned Grants Management Specialist and responsiveness by components of participating organizations, FDA. Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed.

Post Submission Materials
Applicants are required to follow the instructions for post-submission materials, as described in NOT-OD-13-030.

Section V. Application Review Information

1. Criteria
Only the review criteria described below will be considered in the review process.

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

Significance (25 Points)
Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s) (20 Points)
Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation (10 Points)

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach (25 Points)

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or FDA-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment (20 Points)

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items, but will not give separate scores for these items and should not consider them in providing an overall score.

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.

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or FDA-defined clinical research, 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 to determine if it is justified in terms of the scientific goals and research strategy proposed. For

additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research.

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

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

Not Applicable.

Renewals

Not Applicable.

Revisions

Not Applicable.

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.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: (1) Data Sharing Plan; (2) Sharing Model Organisms; and (3) Genomic Data Sharing Plan (GDS)

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

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.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by an Objective Review Committee using the stated review criteria.

As part of the objective review, all applications:

- Will receive a written critique.

Appeals of objective review will not be accepted for applications submitted in response to this FOA.

The following will be considered in making funding decisions:

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

3. Anticipated Announcement and Award Dates

Successful applicants will be notified of additional information that may be required or other actions leading to an award. The decision not to award a grant, or to award a grant at a particular funding level, is discretionary and is not subject to appeal to any FDA or HHS official or board.

Section VI. Award Administration Information

1. Award Notices

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's 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.

Any application awarded in response to this FOA will be subject to terms and conditions found in the HHS Grants Policy Statement.

2. Administrative and National Policy Requirements

All FDA grant and cooperative agreement awards include the *HHS Grants Policy Statement* as part of the NoA.

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English

proficiency. Please see http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html; and http://www.hhs.gov/ocr/civilrights/understanding/index.html. Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html. Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53.

FDA considers the sharing of research resources developed through FDA-sponsored research an important means to enhance the value and further the advancement of research. When research resources have been developed with FDA funds and the associated research findings published, those findings must be made readily available to the scientific community.

Upon acceptance for publication, scientific researchers must submit the author's final manuscript of the peer-reviewed scientific publication resulting from research supported in whole or in part with FDA funds to the NIH National Library of Medicine's (NLM) PubMed Central (PMC). FDA defines the author's final manuscript as the final version accepted for journal publication, which includes all modifications from the publishing peer review process. The PMC archive is the designated repository for these manuscripts for use by the public, health care providers, educators, scientists, and FDA. Please see the FDA Public Access Policy.

Additional terms and conditions regarding FDA regulatory and Center for Biologics Evaluation and Research (CBER) programmatic requirements may be part of the Notice of Award.

Cooperative Agreement Terms and Conditions of Award

The administrative and funding instrument used for this program will be the cooperative agreement an "assistance" mechanism (rather than an "acquisition mechanism"), in which substantial FDA programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, FDA's objective is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipient in a partnership role; it is not to assume direction, prime responsibility, or a dominant role of activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardee for the project as a whole, although specific tasks and activities may be shared between the awardee and FDA as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

The Principal Investigator/Program Director (PD/PI) will have the primary responsibility for and dominant role in planning, directing, and executing the proposed project, with FDA staff being substantially involved as a partner with the PI.

Awardee will retain custody of and have primary rights to the data and software developed under this award, subject to Government rights of access consistent with current DHHS, PHS, and FDA policies.

An FDA Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

The FDA Project Scientist will monitor the project-related activities of the grantee periodically. The monitoring may be in the form of telephone conversations, emails, or written correspondence between the Project Scientist and the PD/PI. Periodic site visits with the PD/PI and other officials of the grantee organization may also occur. The results of these monitoring activities will be recorded in the official cooperative agreement 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 that state that future funding will depend on recommendations from the FDA Project Scientist. In addition,

a. FDA will have prior approval of the appointment of all key administrative and scientific personnel proposed by the grantee.

b. FDA will be directly involved in the guidance and development of the program.

The FDA Project Scientist will participate, with the grantee, in determining and carrying out scientific and technical activities. Collaboration will also include data analysis, interpretation of findings and, where appropriate, co-authorship of publications.

In addition to the Project Scientist, an FDA Program Official will be responsible for normal stewardship of the cooperative agreement, and will be named in the Notice of Award.

Dispute Resolution:

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and FDA may be brought to Dispute Resolution. A Dispute Resolution Panel will be convened and will have three members: a designee of the Steering Committee chosen without FDA staff voting (where a Steering Committee has not been formed, the awardee shall designate this member), one FDA designee, and a third designee with expertise in the relevant area who is chosen by the other two members; in the case of individual disagreement, the first member may be chosen by the awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) annually and financial statements as required in the Notice of Award.

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.

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 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: http://grants.nih.gov/support/ (preferred method of contact)
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 CenterTelephone: 800-518-4726

Web ticketing system: https://grants-portal.psc.gov/ContactUs.aspx
Email: support@grants.gov

Scientific/Research Contact(s)

Scientific Program Coordinator
Gopa Raychaudhuri, Ph.D.
Senior Scientist
CBER Liaison to WHO
Office of the Director
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO71, Room 7250
Silver Spring, Maryland 20993
Telephone: 240-402-8000
Email: Gopa.Raychaudhuri@fda.hhs.gov

Project Officer
Leslie Haynes, RD
Foreign Regulatory Capacity Building Coordinator
International Program
Office of the Director
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration
10903 New Hampshire Avenue, WO71, Room 7222
Silver Spring, Maryland 20993
Telephone: 240-402-8074
Email: Leslie.Haynes@fda.hhs.gov

Objective Review Contact(s)

Bryce Jones
Office of Acquisitions & Grants Services (OAGS)
Food and Drug Administration
Telephone: 240-402-2111
Email: Bryce.Jones@fda.hhs.gov

Financial/Grants Management Contact(s)

Bryce Jones
Office of Acquisitions & Grants Services (OAGS)
Food and Drug Administration
Telephone: 240-402-2111
Email: Bryce.Jones@fda.hhs.gov

Section VIII. Other Information

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

Authority and Regulations

Awards are made under the authorization of Sections 301 of the Public Health Service Act as amended (42 USC 241) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.