4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-0009]

Cooperative Agreement to Support Innovation in Vaccine Clinical Trial Design and Collaboration in Pharmacovigilance to Advance Global Access to Safe and Effective Vaccines

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces its intention to accept and consider a single source application for an award of a cooperative agreement to the World Health Organization (WHO) in support of collaborative efforts to advance innovative approaches to vaccine clinical trial design and to enhance the utilization of a range of pharmacovigilance tools as a means to further vaccine safety and potentially facilitate more rapid introduction of new vaccines. The goal of FDA's Center for Biologics Evaluation and Research (CBER) is to enhance technical collaboration and cooperation between FDA, WHO, and its Member States to facilitate strengthening regulatory capacity globally.

DATES: Important dates are as follows:

1. The application due date is June 15, 2012.
2. The anticipated start date is September 15, 2012.
3. The expiration date is June 16, 2012.

ADDRESSES: Submit the paper application to: Vieda Hubbard, Grants Management (HFA-500), 5630 Fishers Lane, Rockville, MD 20857, and a copy to Leslie Haynes, Center for Biologics Evaluation and Research, Office of the Director (HFM-30), 1401 Rockville Pike,

Rockville, MD 20852-1448. For more information, see section III of the SUPPLEMENTARY INFORMATION section of this notice.

FOR FURTHER INFORMATION CONTACT:

Gopa Raychaudhuri,

Office of the Director (HFM-1),

Food and Drug Administration,

1401 Rockville Pike,

Rockville, MD 20852,

301-827-6352,

email: gopa.raychaudhuri@fda.hhs.gov.

or

Leslie Haynes,

Office of the Director (HFM-30),

Food and Drug Administration,

1401 Rockville Pike,

Rockville, MD 20852,

301-827-3114,

email: leslie.haynes@fda.hhs.gov.

or

Vieda Hubbard,

Office of Acquisitions and Grants Services (HFA 500),

Food and Drug Administration,

5630 Fishers Lane,

Rockville, MD 20857,

301-827-7177,

email: vieda.hubbard@fda.hhs.gov.

For more information on this funding opportunity announcement (FOA) and to obtain detailed requirements, please refer to the full FOA located at http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm297861.htm.

SUPPLEMENTARY INFORMATION:

I. Funding Opportunity Description

RFA-FD-12-022

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A. Background

CBER has been a leader and active participant in the global community to improve human health in the world's populations over many years. A significant area of engagement for CBER is its support of innovative science to advance vaccine development and to improve access of the global population to safe and effective vaccines. The U.S. Department of Health and Human Services (HHS) has invested significantly in developing sustainable global vaccines production capacity. Adequate regulatory oversight throughout the vaccine development life cycle is essential in assuring the safety, purity, and potency of vaccines and other biologicals.

WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends. It is the

only organization with the mandate, technical expertise, and broad reach to meet the Summary Objectives.

WHO has played a key role for over 50 years in establishing international guidelines and standards for development and use of vaccines and other biologicals. The assessment, licensure, regulatory control, and surveillance of vaccines and biological medicinal products are major challenges for 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). With the globalization of markets, the volume of vaccines and biological medicinal products crossing national borders continues to rise, making it even more critical that regulatory knowledge and experience be shared as appropriate to do so, and that global monitoring to ensure product safety be harmonized to the greatest extent possible.

WHO played a leading role in coordinating pharmacovigilance activities and exchange of information among regulators and public health authorities during the H1N1 pandemic. WHO has further demonstrated its leadership in the cause of vaccine safety through its Global Vaccine Safety Blueprint effort, a WHO initiative that focuses on monitoring vaccine safety once a product has been licensed for use. The Blueprint focuses on the need to monitor vaccinated populations for the occurrence of adverse events following immunization (AEFI), and to address vaccine safety concerns in a timely manner when they arise.

CBER has been a leader and active participant in the global community to improve human health in the world's populations over many years. Its international engagements have been informed by the knowledge that protection of global public health against infectious disease threats translates into protection of public health in the United States. In its capacity as a Pan

American Health Organization/WHO Collaborating Center for Biological Standardization, CBER has supported many of WHO's efforts to advance vaccine safety, including serving on the Consultative Committee of the Global Vaccine Safety Blueprint project, serving on the WHO Global Advisory Committee on Vaccine Safety, and collaborating with the Uppsala Monitoring Center (UMC), a WHO Collaborating Center that is responsible for maintaining the global Adverse Drug Reaction database, Vigibase.

CBER seeks to support efforts to advance innovative approaches to vaccine clinical trial designs and to enhance the utilization of a range of pharmacovigilance tools as a means to further vaccine safety and potentially facilitate more rapid introduction of new vaccines. The two primary focus areas are:

1. Innovative Vaccine Clinical Trial Design

Clinical trials are performed to evaluate the safety and efficacy of vaccines. Improving the efficiency of vaccine clinical trials in the development process could lead to more rapid availability of new vaccines. In the case of early phase clinical trials, new approaches can more rapidly determine whether novel vaccine candidates are likely to be safe and efficacious, and better approaches to optimizing allocation of study participants between late phase clinical trials and postmarketing safety studies could lead to more rapid access to lifesaving vaccines, while still obtaining the data necessary to ensure vaccine safety.

2. Vaccine Pharmacovigilance

An important regulatory tool to assure vaccines are safe and effective is a robust pharmacovigilance system. The decision to license a product is based on information available at the time of approval, and the conditions for use are specified in the product label. However, the knowledge related to the safety profile of the product can change over time through expanded

use in greater numbers of people and in diverse populations. Rare adverse events often are not identified in clinical trials since the numbers of subjects enrolled in the trials are not large enough to detect low frequency signals. Thus, it is essential to continue monitoring vaccine safety throughout the product life cycle and to obtain and analyze any additional safety information in "real time."

This project represents a collaborative effort between CBER and WHO (and complements and builds upon other existing commitments of FDA and HHS with WHO) to support scientific collaboration and enhance regulatory capabilities of National Regulatory Authorities to advance global access to safe and effective vaccines and other biologicals that meet international standards. This project will lead to improved technical cooperation between FDA, WHO, and its Member States.

B. Research Objectives

1. Innovative Vaccine Clinical Trial Design

In recent years there has been interest in finding innovative study designs to speed development of promising new vaccines, particularly in disease areas where an urgent and unmet need exists. Diseases such as malaria, tuberculosis, and human immunodeficiency virus are especially challenging due to the widespread public health impact of these diseases, as well as the fact that traditional vaccine development mechanisms do not appear applicable because of the nature of the disease pathogens and/or the natural history of the disease. Bringing these candidate vaccines forward into larger late Phase 2 or Phase 3 clinical trials has had minimal success to date. The goals, thus, in seeking innovative trial designs are to: (1) Minimize the number of ineffective candidate vaccines that proceed into late Phase 2/Phase 3 trials, (2) enhance ability to identify promising candidate vaccines early to move forward into late Phase

trials, (3) obtain answers to other scientific questions of interest (e.g. establishing correlates of protection) more quickly, and (4) promote more efficient use of resources. Of special interest are various types of adaptive trial designs and other innovations in clinical study designs.

2. Improving Allocation of Safety Data Collection Throughout the Vaccine Development Life Cycle

Achieving optimal allocation of safety data collection at each phase of the product development life cycle requires a better understanding of the interplay among disease morbidity and mortality, vaccine effectiveness and safety, quality of study designs, individual risk perception, and vaccination choice. One approach to obtain this understanding is through mathematical simulation of the vaccine development life cycle. Additional research in both the structure of the mathematical models and how to decide what constitutes the acceptable vaccine risk is needed to advance this work. Further translation of such theoretical work into practical study designs and pharmacovigilance activities through demonstration projects would also be desirable.

3. Enhancing Postmarketing Surveillance of Vaccine Safety

Four types of activities are of interest:

a. Improvement of the evaluation of centralized spontaneous reporting systems data. Efficient and rigorous analysis of spontaneous reports of adverse events following immunization, maintained at the UMC, through improvements in application of case definitions, data mining algorithms, vaccine dictionaries, and development of case-based reasoning strategies (such as text mining and natural language processing and statistical and mathematical algorithms), and other approaches would be considered.

b. Improvements in the interoperability of global pharmacovigilance systems. Examples include the development and implementation of a database that would allow tracking global distribution and use of any vaccine (including vaccine constituents and dose information) and enable linkages to existing global pharmacovigilance systems where those vaccines are in use, as a basis for rapid response to vaccine safety concerns arising in any country where a vaccine is distributed. For countries that have electronic population-based health care data systems, this could include improvements in data architecture (e.g. use of electronic medical records), methods for near real-time surveillance, and conducting definitive studies with rigorous case definitions in an efficient manner for vaccine safety surveillance following globally accepted standards to help create a global vaccine safety data link.

c. Improving approaches to rigorous vaccine safety studies in low and middle income countries (LMICs). The basic requirements for a collaborative approach of this kind in LMICs would be: That the methodology is simple, so it could be easily implemented and standardized for all sites; is timely; only uses resources already available in the local public health system; and avoids the need for population denominators. An example of successful use of this approach is the 2009 H1N1 influenza vaccine safety study using the self-controlled case series methodology. Improving this approach, because of its flexibility and applicability to countries where population denominator information may not be available, is one direction that could be taken.

d. Evaluating social media and mobile communication devices for vaccine safety in LMICs. The use of social media for public health information has received attention recently because of the success of "Google flu trends" (http://www.google.org/flutrends/) and "HealthMaps" (http://healthmap.org/en/) in identifying infectious disease outbreaks, at least as fast as traditional methods but at lower cost. Evaluation of methods for efficient approaches to

aggregating the highest quality information from the Internet and social media for earlier warning of emerging safety concerns or identifying geographically localized clusters for regulators and public health authorities, might be beneficial. Mobile communication devices have been successfully used for drug safety surveillance in Africa. Evaluation of mobile devices for inexpensive alerting of central monitoring point for AEFI might be warranted. The collation, investigation, and analysis of such reports remains a challenge but might be resolved by the development and deployment of artificial intelligence systems to conduct data mining and semiautomated case-series evaluations that would provide cogent summaries for human review.

4. Dissemination of Successful Enhancements to the Vaccine Clinical Trial and Pharmacovigilance Enterprise Through Seminars or Other Training Programs

C. Eligibility Information

WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends. It is the only organization with the mandate, technical expertise, and broad reach through its Member States to meet the project goals.

II. Award Information/Funds Available

A. Award Amount

CBER anticipates providing in FY2012 up to $2 million (total costs include direct and indirect costs) for one award subject to availability of funds in support of this project. The possibility of 4 additional years of support up to $10 million of funding is contingent upon successful performance and the availability of funds.

B. Length of Support

The support will be 1 year with the possibility of an additional 4 years of noncompetitive support. Continuation beyond the first year will be based on satisfactory performance during the preceding year, receipt of a noncompeting continuation application, and available Federal Fiscal Year appropriations.

III. Paper Application, Registration, and Submission Information

To submit a paper application in response to this FOA, the applicant should first review the full announcement located at http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm297861.htm. (FDA has verified the Web site addresses throughout this document, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.) Persons interested in applying for a grant may obtain an application at http://grants.nih.gov/grants/funding/phs398/phs398.html. For all paper application submissions, the following steps are required:

- Step 1: Obtain a Dun and Bradstreet (DUNS) Number
- Step 2: Register With Central Contractor Registration

Steps 1 and 2, in detail, can be found at http://www07.grants.gov/applicants/organization_registration.jsp. After you have followed these steps, submit the paper application to: Vieda Hubbard, Grants Management (HFA-500), 5630 Fishers Lane, Rockville, MD 20857, and a copy to Leslie Haynes, Center for Biologics Evaluation and Research, Office of the Director (HFM-30), 1401 Rockville Pike, Rockville, MD 20852-1448.

Dated: May 10, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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