Overview Information

Agency Name: Department of Health and Human Services, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland, 20993

Issuing Office: Department of Health and Human Services, Food and Drug Administration, Office of Acquisitions & Grants Service, 5630 Fishers Lane, Rockville, MD 20857

Research Opportunity Title: Food and Drug Administration Broad Agency Announcement for the Advanced Research and Development of Regulatory Science

Announcement Type: Broad Agency Announcement

Eligible Applicants: This BAA is open to ALL responsible sources. Offerors may include single entities or teams from private sector organizations, Federally Funded Research and Development Centers (FFRDCs) (see page 4 for FFRDC eligibility requirements) and academic institutions.

Research Opportunity Description: The Food and Drug Administration (FDA) solicits for advanced research and development proposals to support regulatory science and innovation. The FDA anticipates that research and development activities awarded under this BAA will serve to advance scientific knowledge to accomplish its mission to protect and promote the health of our nation.

Types of instruments that may be awarded: Procurement Contracts

Notes: Regarding Funding

In order to ensure enough time to conduct the two-tiered evaluation described in Section IV and still be considered for an award within the current fiscal year, prospective Offerors are encouraged to submit white papers no later than March 30, and earlier if possible. White papers submitted after that date will still be accepted, but due to a lack of lead time, cannot be guaranteed consideration for an invitation to submit a full proposal, and subsequently, potential award within the current fiscal year (which ends September 30, 2019).
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INTRODUCTION

Advancing Regulatory Science and Innovation

This Broad Agency Announcement (BAA), which sets forth research areas of interest for Food and Drug Administration, is issued under the Federal Acquisition Regulation (FAR) part 35.016(c). The purpose of this BAA is to provide a mechanism by which FDA can utilize industry’s and academia’s capabilities to advance the state of the art and achieve improvements in technology, materials, processes, methods, devices, or techniques in specific topics as described in this document. Proposals selected for award are the result of full and open competition and in full compliance with the provision of Public Law 98-369, “The Competition in Contracting Act of 1984” and subsequent amendments.

The FDA protects and promotes the health and safety of all Americans through enhancing the availability of safe medical products and foods and promoting innovation that addresses unmet medical and public health needs. FDA also protects and promotes the health and safety of animals through assuring the availability of safe animal drug products and food. Since 2009, FDA has worked to reduce the harm from all regulated tobacco products. FDA is a science-based regulatory agency and a critical component to the success of the nation’s public health, health care systems, and economy. FDA was created in 1906 as one of our nation’s principal consumer product protection agencies, and is now responsible for assuring the safety of biologics, such as blood products and vaccines, drugs, medical devices, foods, cosmetics, and many other consumer goods.

In the US, FDA-regulated products account for about 25 cents of every dollar spent by American consumers each year — products that touch the lives of every American daily. FDA is responsible for advancing the public health by helping to speed innovations that make foods safer and make medicines and devices safer and more effective. At the same time, FDA helps consumers and health care providers get the accurate and science-based information they need to make the best possible decisions about their use of medical products and foods. FDA is working to protect Americans from tobacco-related death and disease. FDA must make decisions based on the best available scientific data and using the best tools and methods available to ensure products meet the highest quality standards for consumers, while at the same time fostering and advancing innovation in the products it regulates.

The core responsibility of FDA is to protect consumers by applying the best possible science to its regulatory activities — from pre-market review of efficacy and safety of many of its regulated-products; to post-market product surveillance to review of product quality; to regulation of the manufacture, distribution and marketing of tobacco products. In the last few years, rapid advances in innovative science have provided new technologies to discover, manufacture and assess novel medical products, and to improve food safety and quality; FDA must keep pace with and utilize these new scientific advances to accomplish its mission to protect and promote the health of our nation.

The BAA is open to all responsible sources. Offerors may include single entities or teams from private sector organizations, Federally Funded Research and Development Centers (FFRDCs), and academic institutions. Non-U.S. organizations and/or individuals may participate to the
extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances.

Federally Funded Research and Development Centers (FFRDCs) and Government entities (e.g., Government/National laboratories, military educational institutions) are subject to applicable direct competition limitations and cannot propose to this BAA in any capacity unless they meet the following conditions:

1. Clearly demonstrate that the proposed work is not otherwise available from the private sector.
2. Provide a letter on official letterhead from their sponsoring organization citing the specific authority establishing their eligibility to propose to Government solicitations and compete with industry, and their compliance with the associated sponsoring agreement and terms and conditions.

Historically Black Colleges and Universities (HBCU), Minority Institutions (MI), Small Business concerns, Small Disadvantaged Business concerns, Women-Owned Small Business concerns, Veteran-Owned Small Business concerns, Service-Disabled Veteran-Owned Small Business concerns, and HUB Zone Small Business concerns are encouraged to submit proposals and to join other entities as team members in submitting proposals.

The purpose of this BAA is to solicit proposals that focus on one or more of the following areas of interest as listed here and further described in Part I of this announcement.

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthening Social and Behavioral Science at FDA by Enhancing Audience Understanding
9. Strengthening the Global Product Safety Net

Multiple awards are anticipated. The amount of resources made available for individual contract awards under this BAA will depend on the quality of the proposals received and the availability of funds. All funding is subject to government discretion and availability.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this solicitation, and to make awards without discussions with proposers. The Government also reserves the right to conduct discussions if it is later determined to be necessary. If warranted, portions of resulting awards may be segregated into pre-priced/severable options. Additionally, FDA reserves the right to accept proposals in their entirety or to select only portions of proposals for award. In the event FDA desires to award only portions of a proposal, negotiations may be opened with that proposer. The Government reserves the right to fund proposals in phases with options for continued work at the end of one or more of the phases.
To be eligible for award, a prospective recipient must meet certain minimum standards pertaining to financial resources, ability to comply with the performance schedule, prior record of performance, integrity, organization, experience, operational controls, technical controls, technical skills, facilities, and equipment.

This BAA is available on the following websites:

https://www.fbo.gov

This BAA is a continuously open announcement valid throughout the period from the date of issuance through the closing date specified in fbo.gov. Amendments to this BAA will be posted to www.fbo.gov when they occur. Interested parties are encouraged to periodically check these websites for updates and amendments.

Part I: Research Areas of Interest

Through this BAA, FDA seeks to support advanced research and development strategies in the following research areas of interest. This section presents the technical objectives that FDA seeks to achieve through this BAA. Offerors should propose a Statement of Work (SOW) that is consistent with research and development work as defined in FAR 35.001. Proposal preparation and submission instructions are contained in Part III.

1. Modernize Toxicology to Enhance Product Safety

FDA seeks to improve the toxicologic and pharmacologic tools used to minimize risk and evaluate product safety and efficacy by conducting internal and collaborative research and development. Areas of interest include:

1.1 Develop better models of human and animal (where applicable) adverse response:

- 1.1.1 Evaluate and promote the use of cell- and tissue-based assays that more accurately represent human susceptibility than animal models to adverse reactions;

- 1.1.2 Develop new animal models that better mimic diseases to better understand the potential influence of disease progression and disease co-morbidities on the emergence of adverse events;

- 1.1.3 Promote a better understanding of toxicity mechanisms by evaluating safety assessment data at multiple levels of biological organization including genes, proteins, pathways, and cell/organ function;

- 1.1.4 Assess and characterize molecular targets, host genetic and inflammatory factors that may be associated with rare and unexpected adverse events (“off-target” drug effects);

- 1.1.5 Initiate in vitro and in vivo studies to identify potential biomarkers of harm associated with exposure to tobacco products or tobacco product constituents; and the onset of tobacco related diseases; and
1.1.6 Initiate *in vitro* studies to identify potential markers of harm associated with exposure to medical products.

1.1.6.1 Using in vitro and in vivo methods, assess toxicological implications of electronic nicotine delivery systems (ENDS) products considering aerosol chemistry (e.g., HPHCs), e-liquid composition (e.g., flavors, PG/VG ratio), and aerosolization methods (e.g., wicking systems and voltage delivery)

1.1.7 Develop methods for biocompatibility and toxicological risk assessments for new device materials in line with public policies of e.g. Least Burdensome measures and the reduction in the use of animals.

1.1.8 Develop methods that facilitate the use of cell- and tissue-based assays that more accurately assess human adverse response to ingredients in dietary supplements

1.1.9 Develop computational modeling and simulation methods to promote the use of in silico assessment of devices and materials

1.1.10 Develop in vitro methods that can more accurately predict in vivo responses resulting from exposure to ENDS and other tobacco products or their constituents

1.1.11 Develop new methods that can assess toxicokinetics and toxicodynamics of nicotine across different routes of exposure and its contribution to cancer and non-cancer toxicological risk

1.1.12 Develop models for the prediction of respiratory tract deposition of smoke/aerosol particulates, their retention, sites of deposition in relation to respiratory and cardiovascular outcomes

1.2 Identify and evaluate biomarkers and endpoints that can be used in non-clinical and clinical evaluations:

1.2.1 Evaluate the accuracy (specificity and sensitivity) with which animal models and *in vitro* assays correctly predict potential human and animal risk;

1.2.2 Assess concordance between animal and human biomarkers of toxicity and determine how the performance of these biomarkers and their interpretation may vary across different organ systems and human populations; and

1.2.3 Evaluate quantitative imaging (e.g. positron emission tomography, magnetic resonance imaging, computed tomography) and other advanced approaches (e.g. metabolomics) for identifying new biomarkers and predictors of efficacy and adverse responses of novel materials and chemicals.

1.2.4 Investigate precision medicine and biomarkers for predicting medical device performance, disease diagnosis and progression.

1.2.5 Evaluate the biomarkers and the role of the microbiome in contributing to adverse responses through alterations in metabolism or other mechanisms

1.2.6 Evaluate critical toxicity mechanisms and modes of action for key constituents of ENDS and other tobacco products, including HPHCs that drive cancer and non-
cancer toxicological risk

1.2.7 Identification and assessment of characteristics, design features, ingredients and topography of a wide variety of ENDS products that could affect HPHC production and potential risk to users

1.3 Use and develop computational methods and in silico modeling:

1.3.1 Improve the value of chemical Structure-Activity Relationship (SAR) models in the prediction of human risk.

1.3.2 Develop, validate and implement approaches to link chemical structures and substructures to information about product risk and safety, disease targets, and toxicity mechanisms;

1.3.3 Develop clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes;

1.3.4 Develop computer models of cells, organs, and systems to predict product risk, safety and efficacy;

1.3.5 Develop computer models that integrate pharmacokinetic, pharmacodynamic, materials science, or mechanistic safety data to predict clinical risk and corroborate post-market findings in different patient populations; and

1.3.6 Develop and apply data mining, knowledge building, and data visualization tools to inform computer model development, clinical risk prediction, and regulatory decision-making.

1.3.7 Develop computer models for assessing the risk of new tobacco products that will potentially enter the market by considering potential risks to users of the products and users’ demographic attributes and usage patterns.

1.3.8 Develop data analysis techniques and perform data profiling in order to improve overall regulatory data quality and support mathematical, statistical modeling and analysis capabilities to derive enhanced analytical results for human drug regulatory operations.

1.3.9 Develop innovative models for effectively correlating in vitro data to in vivo findings for the assessment of human health risk resulting from exposure to ENDS and other tobacco products or their constituents.

1.3.10 Develop computer models of cells, organs, and systems to predict risk and safety of ingredients in dietary supplements, including potential interactions with drugs and other dietary supplements.

1.3.11 Develop predictive toxicology tools that can integrate multiple types of data from in vitro and in vivo studies regarding ENDS and other tobacco products into a unified risk assessment paradigm.
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes

FDA seeks to develop new tools and approaches needed to catalyze the development of personalized medicine and to modernize and advance the science and conduct of clinical trials. Areas of interest include:

2.1 Develop and refine clinical trial designs, endpoints and analysis methods:

2.1.1 Refine clinical trial design and statistical methods of analysis to address issues such as missing data, multiple endpoints, composite endpoints, patient enrichment, and adaptive designs;

2.1.1.1 Refine or develop statistical clinical trial designs and data analyses methods for leveraging data from external sources such as historical studies, registries, patient-generated health data, insurance claims, electronic health records and pre-clinical studies;

2.1.1.2 Develop and validate statistical program packages for innovative clinical trial designs and data analyses;

2.1.2 Identify and evaluate improved clinical endpoints and related biomarkers for trials in areas where optimal endpoints are lacking (e.g., efficacy and safety endpoints for osteoarthritis in humans and animals, for gene therapy, for transplant-related studies (endpoints and duration), for ophthalmic indications, for tumor vaccines, and for stem cell-derived therapies);

2.1.3 Develop novel trial designs and endpoints for special needs (e.g., small trials for orphan indications, designs and endpoints for pediatric trials including neonatal trials);

Pilot research to assess the impact of Accelerated approval (AA), and Fast track (FT), priority review (PR), and Breakthrough (BT) designations to help assess adequacy of pre-market efficacy and safety assessments and the generalizability of the findings from smaller clinical trial populations to larger more diverse populations. The impact of incentives for the respective programs such as marketing exclusivity, priority review vouchers and the application of flexibility and scientific judgment available under existing regulations needs to be assessed. The intent is to identify factors or metrics that may further enhance drug development and safe and effective use post-approval. Approaches include:

A. Assessing the adequacy of currently available data sources to conduct appropriate analyses and tracking and
B. Identifying appropriate comparators for assessing impacts.
C. Identifying factors either common for all or particular to each expedited program that can assess:
   • Safety of the drugs in the post-approval period (e.g., higher numbers/rates of withdrawals, adverse events reported, or serious labeling changes for safety, such as a boxed warning or restricted indication)
   • Timelines, achievement of milestones or costs during drug development
   • Application of novel or innovative clinical trial designs and data analyses
   • Clinical trial population sizes and diversity; drug, disease, or program
attributes (such as available natural history studies or registries, patient-advocacy involvement, funding sources, drug class or disease precedent)
- Pricing and accessibility post-approval; and effectiveness post-approval
- In particular for orphan drugs, effectiveness of programs and incentives to address unmet medical needs in the rare disease population and FDA’s use of flexibility for rare disease drug development and approvals

2.1.4 Continue to refine the use of modeling and simulation in clinical trial design to enhance the effectiveness of clinical studies; and

2.1.5 Develop practical methods to determine the absolute or comparative effectiveness of patient-matched medical products

2.1.6 Develop educational materials to enhance FDA’s capacities to conduct review of clinical outcome assessments (and their resulting endpoints), including patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcomes.

2.1.7 Identify and evaluate good practices of patient involvement in clinical study design and conduct.

2.2 Leverage existing and future data:

2.2.1 Develop quantitative models and measures of disease progression; and

2.2.2 Utilize large, pooled clinical trial datasets to identify potential trial endpoints, explore differences in specific populations and subpopulations (e.g., stage of disease, chronic disease states, sex, race and ethnicity, pediatrics and age groups) and different subsets of diseases, improve understanding of relationships between clinical parameters and outcomes, and evaluate clinical utility of potential biomarkers.

2.2.3 Develop new tools and methodologies to harness big data and real-world data (e.g. data derived from electronic health records (EHRs); medical claims ad billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices) to support regulatory decision-making.

2.2.4 Survey existing and develop new statistical methods for synthesizing data from various sources such outside of US studies, historical studies, and registries.

2.2.5 Advance methodologies to generate clinical evidence from real world data sufficient to support regulatory use
- Incorporate real world data sources in innovative clinical trial designs
- Develop and validate tool and models that assess fitness of real world data to support regulatory decision making
- Develop and validate methods to predict device performance using real world data
- Identify high priority areas for development of real-world data source methodology that meet stakeholder needs using a collaborative approach
2.2.6 Develop core data elements and data sets for device categories to support regulatory decision making

2.2.7 Develop standards for data quality and data sources that increase the quality, interoperability, and usability of real-world data

2.2.8 Design and optimize data infrastructure to facilitate information exchange and data extraction

2.3 Identify and qualify biomarkers and study endpoints:

2.3.1 Facilitate identification and qualification of new and improved biomarkers for safety and efficacy, pharmacodynamic response - dose selection, disease severity, progression and prognosis, and pharmacogenomics (to predict safety and efficacy or guide dosing); and

2.3.2 Develop and evaluate novel approaches for biomarker identification, including -omics, systems biology, and high throughput methods.

2.3.3 Develop robust techniques to evaluate the ability of patient-matching processes (e.g. algorithms, workflows, software) used to fit implants and surgical guides across the variability within a desired population.

2.4 Facilitate Antibacterial Drug Development and Address Antibacterial Drug Resistance

Antibacterial drug resistance is a major threat to public health. FDA’s roles in combatting antibacterial drug resistance are to: (1) facilitate the development of new antibacterial drugs to treat patients and (2) advance the science of clinical trial design. FDA is interested in the following topic areas:

2.4.1 Evaluate potential innovations in clinical trial design for new antibacterial drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches

2.4.2 Advance the science of in-vitro, animal model, and/or pharmacokinetic studies to facilitate antibacterial drug development, including studies focused on drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction

2.4.3 Evaluate strategies to enrich enrollment in clinical trials for new antibacterial drugs such as the use of rapid diagnostic tests

2.4.4 Advance the science of antibacterial drug susceptibility testing

2.5 Facilitate Drug Development and Appropriate Use for Patients with Serious Mental Illness.

Serious Mental Illness (SMI) is a major threat to public health. FDA’s roles in addressing SMI include: (1) facilitating the development of new therapies to treat patients, (2)
advancing the science of clinical trial design, including identification of biomarkers, and (3) developing a better understanding the performance of available therapies, including the specific risks and benefits in specific populations, including those with comorbid diagnoses, such as substance abuse and dependence. FDA is interested in the following topic areas:

2.5.1 The development and refinement of clinical trial designs, endpoints, and analysis methods that could be used for SMI drug development. This includes the topics listed above in Section 2.1, but should consider and specifically be tailored to SMI drug development. Of interest also are specific approaches that could be used to support the development of treatment options for pediatric patients with SMI.

2.5.2 The development or enhancement of clinical trial networks, platforms, and/or registries to study new or existing drugs for SMI for patients of all ages. This includes the conduct of randomized trials, including pragmatic design trials, or observational or natural history studies within these networks, platforms, and/or registries to inform patients and prescribers about the appropriate use of medications for SMI and to facilitate new drug development.

2.5.3 The identification and qualification of biomarkers or other study endpoints that could be used for SMI drug development. This includes the topics listed above in Section 2.3, but should consider and specifically be tailored to SMI drug development, including pediatric patients.

2.5.4 The development of approaches to better identify patients who would benefit from treatment with drugs intended for SMI or to encourage increased compliance with SMI drug treatment, including pediatric patients.

2.6 Facilitate Development of Drug Therapies for Youth Tobacco Cessation

Despite major progress over the past half-century, tobacco use remains the leading cause of preventable disease and death in the United States, with at least 480,000 people dying prematurely each year from diseases caused by cigarette smoking or secondhand smoke exposure.\(^1\) Nearly all tobacco product use begins during youth and young adulthood.\(^2\) While the current use of any tobacco product among U.S. middle and high school students has decreased from 2011-2017, there has been an alarming increase in e-cigarette use over this time. In fact, since 2014, e-cigarettes have been the most commonly used tobacco products among youth, used by 1.73 million (11.7%) high school students and 390,000 (3.3%) middle school students in 2017.\(^3\) Youth e-cigarette use raises a number of health concerns including risk of addiction to nicotine, potential harm to the developing adolescent brain, and exposure to chemicals including carbonyl compounds and volatile organic compounds known to have adverse health effects; the full range of possible health effects is not yet completely understood.\(^4\)

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2 Ibid.


4 US Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults: A Report of the
In addition to the prevention of initiation, which will be the cornerstone of any successful effort to curb youth tobacco use, FDA is also exploring additional approaches to address this public health issue. One such approach may be the development of drug therapies, as part of multimodal treatment strategies including behavioral interventions, to support youth tobacco cessation. To date, research on youth tobacco cessation has been limited and focused primarily on cigarette smoking cessation. FDA is interested in the topic areas described below. Of note, we believe that many of these issues will need to be addressed uniquely based on the type of tobacco product being used (e.g., combustible cigarette, e-cigarette, smokeless tobacco). Submissions should indicate what type of tobacco products will be addressed by the research and include justification for any evaluation that combines multiple type of tobacco products.

2.6.1 The development of data or methods to quantify the range of factors that contribute to initiation and continuation of specific tobacco products among youth, as well as youth attitudes towards tobacco cessation.

2.6.2 The development of data or methods to identify youth tobacco users who may benefit from treatment with drugs intended for cessation, either alone or in combination with behavioral interventions. Factors to consider include age (older vs. younger adolescent), patterns of use (duration and frequency of use), clinical features (level of addiction, presence/absence of comorbidities including psychiatric disease), and type of tobacco product.

2.6.3 Identification and analysis of scientific, clinical, and societal factors that could either encourage or impede the conduct of clinical studies designed to evaluate drugs intended for various youth tobacco product cessation. Evaluation of approaches that could be used to overcome identified barriers and encourage research.

2.6.4 The development of methods, measures and study designs appropriate for the evaluation of drug therapies for youth tobacco cessation. Factors to consider include the identification of informative endpoints and the development of assessment tools to evaluate these endpoints.

2.6.5 The development of data or approaches to support the ability to extrapolate data from approved smoking cessation drug therapies for adults to youth tobacco cessation.

3. Support New Approaches to Improve Product Manufacturing and Quality

FDA seeks to support the application of novel technologies to product development and innovative analytical approaches to improve product manufacturing and quality through active research. Areas of interest include:

3.1 Enable development and evaluation of novel and improved materials and manufacturing methods:

3.1.1 Investigate the effects of advanced manufacturing on product quality. Proposals could include research on technologies and materials that:

- Result in manufacturing technology, tools, or approaches that enhance control of critical quality attributes for drug substances or products, or
- Improve manufacturing capabilities for complex drugs as defined within the GDUFA II Commitment Letter.

3.1.2 Examine specific novel material and manufacturing technologies to determine how they impact product failure rates; and

3.1.3 Evaluate complex drug substances and complex drug product dosage forms, especially potential regulatory questions related to drug quality. Some specific areas of research could include the following (1) appropriate analytical methods for complex drug substances or products, (2) in-process controls during manufacturing processes to ensure product quality, and (3) raw material quality control. Proposals should clearly describe the potential impacts of the proposed enabling technology on readiness for broad implementation in pharmaceutical industry, control strategy, and/or regulatory evaluation for complex drug substances and complex drug product dosage forms, including natural products

3.1.4 Explore novel approaches to incorporating medical device development concepts and methodologies, including quality and risk management.

3.1.5 Develop and evaluate practical in-process monitoring systems, methods, and metrics for additive manufacturing processes.

3.1.6 Explore novel application of large-scale continuous manufacturing processes for more complex biologic products, such as vaccines, and cell and gene therapies. Proposals should clearly describe the potential impacts of the proposed enabling technology on readiness for broad implementation in pharmaceutical industry, control strategy, and/or regulatory evaluation of CM, and should clearly quantify the improvement metric for implementation of CM at a commercial scale as compared to batch or pilot production if relevant:

- Closed and automated manufacturing technologies
- Modular platforms for complex biologics manufacturing and testing
- Process modeling and simulation
- Advanced manufacturing technologies for cell cultures used to manufacture vaccines

3.2 Develop new analytical methods:

3.2.1 Investigate feasibility and value of using improved analytical technologies for evaluating product quality of pharmaceutical agents and other regulated products, and evaluate whether these improved technologies should be incorporated into product assessments;

3.2.2 Evaluate applicability of various analytic technologies for determination of the “similarity” of biosimilars to their reference products;

3.2.3 Perform statistical research to support development and evaluation of new assays and tests needed to assure analytical methods give
consistent reproducible results; and

3.2.4 Develop improved methods and tools to detect and measure the physical structure, chemical properties, and biological behavior of engineered nanomaterials, additively manufactured pharmaceuticals (pharmacoprinted products), and complex dosage forms (e.g., transdermal patches, inhalation delivery systems, and targeted drug delivery systems) in FDA-regulated products.

3.2.5 Develop methods to assess quality of glycerin; develop methods to identify the quality (crude vs industrial vs USP) and potential contaminants in the various glycerin grades used in finished products (for e.g. jerky pet treats for animals, drugs for humans and animals).

3.2.6 Advance tests and methods for predicting and monitoring medical device clinical performance.

3.3 Develop assessment tools to support facility and product surveillance and monitoring of quality systems and processes:

3.3.1 Advance the study of quality metrics and quality culture, including pharmaceutical quality systems, manufacturing operations, continuous improvement, and overall quality culture in domestic and international establishments.

3.3.2 Develop methods for data collection, validation, and assessment of such metrics

3.3.3 Advance statistical methodology for assessing disparate data types and sources in the evaluation of products, manufacturing facilities and quality systems and processes

3.4 Reduce risk of microbial contamination of products:

3.4.1 Develop sensitive, rapid, high-throughput methods to detect, identify, and enumerate microbial and chemical contaminants and validate their utility in assessing product sterility; and

3.4.2 Develop and evaluate methods for microbial inactivation/removal from medical products that are not amenable to conventional methods of sterilization.

3.4.3 Enhance safety and performance of reusable devices by improving the quality and effectiveness of antimicrobials, sterilization and reprocessing of medical devices.

3.5 Improve scientific approaches to evaluate generic drugs

In July 2012, Congress passed the Generic Drug User Fee Amendments (Title III of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144)). The Generic Drug User Fee Amendments (GDUFA) is designed to enhance public access to safe, high-quality generic drugs, and to reduce costs to industry. To support this goal, FDA agreed in the GDUFA commitment letter to consult with industry and the public in order to create an annual list of
regulatory science initiatives specific to research on generic drugs for each year covered by GDUFA. This commitment continues in the Generic Drug User Fee Amendments of 2017 (GDUFA II). The research activities related to the FY 2018 topic areas are as follows:

3.5.1 Post-market Evaluation of Generic Drugs

3.5.1.1 Develop surveillance and monitoring methods for generic drug substitutions.

3.5.1.2 Understand patient perceptions of generic drug quality and effectiveness.

3.5.2 Complex active ingredients, formulations, or dosage forms

3.5.2.1 Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients

3.5.2.2 Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

3.5.2.3 Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products

3.5.2.4 Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables including the identification of the critical quality attributes (CQA) for these products

3.5.2.5 Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

3.5.3 Complex routes of delivery

3.5.3.1 Improve Physiologically-Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

3.5.3.2 Expand characterization-based BE methods across all topical dermatological products

3.5.3.3 Expand characterization-based BE methods across all ophthalmic products

3.5.3.4 Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids

3.5.3.5 Develop alternatives to clinical endpoint BE studies for locally-acting nasal products that are more predictive of and sensitive to differences in local delivery

3.5.4 Complex drug-device combinations

3.5.4.1 Evaluate the impact of identified differences in the user-interface from the RLD on the substitutability of complex generic drug-device combination products

3.5.5 Tools and methodologies for bioequivalence and substitutability evaluation

3.5.5.1 Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products

3.5.5.2 Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision-making about generic drug bioequivalence standards
3.5.5.3 Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

3.5.5.4 Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution/utilization patterns and drug safety and quality data) to support regulatory decisions and improve post-market surveillance of generic drug substitution

3.6 Identify and Qualify Pain-Associated Biomarkers that are Associated with Therapeutic Control of Pain in Food Producing Animals

3.6.1 Identify molecular biomarkers (proteomic or genomic) that can be qualified against clinical signs to serve as surrogate endpoints in assessing the capacity of therapeutic agents to alleviate pain in food animals such as cattle, pigs, and goats.

3.7 Develop a Regulatory Database for Species Identification

3.7.1 Develop a DNA barcode sequence database for species identification

3.8 Develop methods to improve the cybersecurity of medical devices

3.8.1 Enhance performance of Digital Health and medical device cybersecurity: Digital Health and cybersecurity are some of the fastest growing areas impacting medical devices. Devices are being increasingly used in networked environments and are expected to communicate with one another securely and accurately. To ensure these technologies and technological environments achieve the desired public health impact, research is needed to enhance performance and security of medical devices and interoperability, and to understand the impact of software modifications on device performance.

Pilot the use of a benchmark test set for the use of artificial intelligence (AI) in medical devices to enhance consistency of submissions and review by enabling AI with similar instructions for use (IFU) to be tested and compared.

1. Develop a full test case and/or methodology for adaptive algorithm use in medical device submissions to help stakeholders to better understand and evaluate use of AI in a medical device context of use.

2. Develop framework on how to structure post launch real world evidence data to support clinical claim modification and provide greater clarity and guidance to industry while potentially streamlining device review.

3. Investigate and evaluate strategies to detect and assess the performance of artificial intelligence (AI) algorithms including employing synthetic data sets, leveraging the Medical Device Development Tool (MDDT) program, identifying novel methods, and conducting statistical analyses of regulatory device submissions to facilitate greater utilization of AI within medical devices.

4. Develop and deploy secure medical device reference architectures that support the needs of the clinical use environment by applying formal methods, leveraging hardware and software reuse, facilitating timely updates and patching, and highlighting failures while collecting forensically sound evidence of performance to improve medical device security at the systems level.

5. Develop methods for efficiently communicating design vulnerabilities such as tools for...
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

FDA seeks to evaluate new and emerging technologies through active research intramurally and collaboratively with external partners. Areas of interest include:

4.1 Develop assessment tools for novel therapies:

4.1.1. Develop new approaches such as in vitro and in vivo methods to identify measurable characteristics of product safety, quality, and potency when evaluating new therapeutics (e.g., engineered tissues or cell therapy products, including stem cell-derived products, for clinical application in regenerative medicine, additive manufacturing in medical products).

4.1.1.1 Identification of critical quality attributes (CQAs) and development of advanced assays for characterization of CQAs in products for cell therapies.

4.1.1.2 Development of reference materials and standards for cell therapies.

4.1.2 Develop new ways to evaluate gene therapy products developed in this period of fast-paced scientific progress;

4.1.2.1 Improved cell lines for viral vector production and improved vector purification technologies.

4.1.2.2 Identification of critical quality attributes (CQAs) and development of advanced assays for characterization of CQAs in products for gene therapies.

4.1.2.3 Development of reference materials and standards for gene therapies.

4.1.3 Integrate an understanding of product quality and safety based on novel genomic, proteomic, metabolomic, and other -omic technologies;

4.1.4 Explore the role of digital health in new medical therapies and diagnostics.

4.1.5 Develop methods for predicting and monitoring clinical performance of devices and materials.

4.1.6 Explore human factors engineering principles in device design and review.

4.2 Develop assessment tools to evaluate packaging, storage, delivery and disposal solutions, as well as product formulations, designed to prevent or deter misuse and abuse of opioid analgesics.

4.2.1. Perform research to enhance FDA’s understanding of the features of existing and emerging packaging, storage, delivery and disposal solutions, how they fit into the
continuum of opioid misuse and abuse, and the evidence available to support these features.

4.2.1. Evaluate whether any existing data requirements in other fields may be applicable for packaging, storage, delivery and disposal solutions to prevent or deter misuse and abuse of opioid analgesics. Exploratory research should include abuse deterrent packaging, medication adherence packaging, or child resistant packaging.

4.2.1.1. Evaluate whether any existing data requirements in other fields may be applicable for packaging, storage, delivery and disposal solutions to prevent or deter misuse and abuse of opioid analgesics. Exploratory research should include abuse deterrent packaging, medication adherence packaging, or child resistant packaging.

4.2.1.2. Research whether there are any existing data requirements in other countries to have packaging, storage, delivery and disposal solutions approved or labeled as being able to prevent or deter misuse and abuse of opioid analgesics.

4.2.1.3. Identify and evaluate appropriate endpoints for studies undertaken to support packaging, storage, delivery and disposal solutions approved or labeled as being able to prevent or deter misuse and abuse of opioid analgesics.

4.2.2. Combine findings from 4.2.1.1 and 4.2.1.2 and work with FDA to define what the data needs and guiding principles should be for industry to follow to have their packaging, storage, delivery and disposal solutions approved or labeled as being able to prevent or deter misuse and abuse of opioid analgesics. Draft and provide to FDA a Final Report for its use.

4.2.3. Perform research to enhance FDA’s understanding of the uptake and use of abuse deterrent opioid product formulations after approval and their impact on patterns of misuse, abuse, addiction, overdose and death in communities, improve our knowledge about the data systems and methods available to study their impact, and develop new data resources and methods in this area.

4.2.3.1. Perform research to enhance FDA’s understanding of the relationship between the number of dispensed prescriptions and abuse rates for opioid products. Relevant activities would include qualitative and/or quantitative research to better understand the reasons for decreases in prescription volume that often occur after the marketing of opioid products reformulated with abuse deterrent properties. Other relevant activities would include qualitative and/or quantitative research to better understand how well local, state, or national drug utilization data reflect availability of, or access to, various opioid products for misuse and abuse in communities.

4.2.3.2. Perform research to enhance FDA’s understanding of existing data systems used to evaluate the impact of abuse deterrent formulations. Relevant activities would include research to better understand factors influencing the use of poison control call centers in settings of drug misuse, abuse, and overdose, and how these factors may drive overall or drug-specific trends in poison control center utilization over time. Other relevant activities would include research to better understand the accuracy of information collected on abuse of specific opioid products and formulations in poison center data or in self-reported data collected from individuals entering or being assessed for substance abuse treatment.

4.2.3.3. Develop new data resources, methods, and linkages to advance the science of evaluating abuse-deterrent opioid products and their impact on misuse, abuse, addiction, overdose and death in communities in the U.S. Examples might include novel methods of collecting, linking, and analyzing data from prescription drug monitoring programs, emergency department and other medical records, administrative claims, surveys, substance abuse treatment programs, syringe exchange programs, and medical examiner databases.

4.3 FDA is interested in trending drug use over time to provide a context for evaluating...
drug safety in pediatric populations. In pediatrics, this requires integrating information from three main sources: free-standing children’s hospitals, pediatric hospitals (or wards) within adult institutions, and general hospitals that also care for children. Prior internal research has shown that these types of institutions may have markedly different pediatric drug utilization patterns. The overall intent is to develop a methodology to provide a comprehensive picture of pediatric drug outcomes to improve utilization, and improve FDA’s ability to assess post marketing utilization and safety in pediatric populations. Deliverables would include:

4.3.1. Identify and have access to appropriate sources for pediatric drug utilization data.

4.3.1.1. Identify and evaluate appropriate variables needed to calculate utilization projections.

4.3.1.2. Evaluate the ability to project to sub-populations of interest (e.g. Age group, disease/condition, geography).

4.3.1.3. Evaluate the ability to present both overall drug utilization data and data based on facility characteristics (e.g. bed size, rural/urban, teaching/non-teaching, other pediatric network characteristics such as satellite outpatient pharmacies in pediatric clinics and/or offices).

4.3.1.4. Evaluate generalizability of the data and flexibility to encompass changes in the composition of either institution or pediatric populations.

4.3.1.5. Evaluate potential differences in inpatient versus outpatient utilization data depending on the size and nature of the pediatric network, such as the use of satellite hospital pharmacies located in wholly-owned pediatric off-site clinics.

4.3.2. Provide robust data analyses across a variety of drugs and drug classes across time to validate the methodologies developed.

4.3.2.1. Develop and provide reports that would enhance the FDA’s knowledge regarding pediatric drug utilization

4.3.3. Identify and have access to sources for pediatric drug safety outcome data.

4.3.3.1. Evaluate drug safety outcome data in both impatient and outpatient pediatric populations

4.3.3.2. Evaluate detailed clinical drug safety outcome data in neonates.

5. Harness Diverse Data through Information Sciences to Improve Health Outcomes

FDA seeks to develop agency information sciences capability. Areas of interest include:

5.1 Develop and apply simulation models for product life cycles, risk assessment, and other regulatory science uses:

5.1.1 Identify opportunities and develop computer simulation and modeling to streamline data analysis and model biological systems and their responses to agents of concern, such as toxins, toxic compounds, pathogens, and biomaterials; and

5.1.2 Promote novel clinical trial design using simulation, new statistical models, and novel animal models/animal model alternatives.
5.1.3 Develop life cycle assessment of newer generations of ENDS products.

5.1.4 Develop methods to estimate the environmental fate of cigarette, cigar butts, and cigarillo tips, including substances leached from discarded butts or tips and their transport in the environment.

5.2 Develop and analyze large scale clinical and nonclinical data sets:

5.2.1 Refine methods for analysis of pre-market and post-market data, including data mining of spontaneous reports and analysis of data accessible from large healthcare databases and electronic health records

5.2.2 Develop methods to harness clinical evidence and evidence synthesis from multiple domains

5.2.3 Develop data mining methods for analyzing standardized electronic data submitted to the Agency such as CDISC SEND (nonclinical) and SDTM/ADAM (clinical) datasets and for extracting data from FDA created reviews and other documents

5.2.4 Leverage real-world evidence and employ evidence synthesis and linkage across multiple domains to support regulatory decision-making

5.2.5 Test and validate innovative computer models and tools on clinical data (e.g. electronic health records and SDTM/ADAM datasets) to evaluate safety of novel drug products; Test and validate innovative computer models and tools on nonclinical data (e.g., SEND) to evaluate safety of novel drug products

5.2.6 Enhance FDA’s capacity to assess death and cause of death as an outcome of product safety and/or effectiveness in large electronic healthcare databases

5.2.7 Develop guidelines for assessment of data quality and study designs for synthesizing data across multiple sources

5.2.8 Develop statistical methods for assisting compliance inspection

5.2.9 Develop systems model of opioid crisis to assess the effectiveness of FDA interventions designed to reduce the frequency or lethality of overdose and opioid use disorder

In November 2017, the FDA Commissioner announced four priority areas to address the opioid crisis. These priority areas include 1. decreasing exposure and preventing new addiction; 2. supporting the treatment of those with opioid use disorder; 3. fostering the development of novel pain treatment therapies; and 4. improving enforcement and assessing benefit-risk. To inform the interventions stemming from these priority areas and to better communicate FDA’s analysis of the crisis, a comprehensive model of the opioid crisis must be built. This model will examine the factors that influence the rate of opioid use disorder and overdose death in the national population.

New research approaches are needed to collect and analyze data, elicit estimates from experts where data is unavailable, and apply them to an existing systems model to show quantitatively how FDA’s opioid interventions influence the rate of opioid use disorder and overdose death. Research approaches should have the potential to incorporate relevant
literature and expert opinion and quantify changes in population outcomes after the implementation of new and existing FDA policies. Research approaches, additionally, should have the potential to produce a quantitative version of an existing qualitative model that is readily updatable and maintainable by FDA staff, and whose key findings can be readily communicated to policymakers and the public. This model will serve as a decision support tool for the FDA in the development and analysis of new policies.

5.2.10 Compare data obtained in the clinical setting capturing information about the physical function of advanced cancer patients collected by various sources including electronic PRO, wearable technologies, performance outcomes and clinician assessment.

(Physical function is an important patient-centered outcome across disease contexts. FDA has identified the use of electronically captured patient-reported outcome (ePRO) physical function scales and wearable technologies as promising drug development tools to inform future development of oncology clinical trial endpoints. The purpose of this research is to conduct a prospective study focusing on measuring changes in physical function throughout the natural history of advanced cancer and its treatment. The study will assess physical function and activity in a group of advanced cancer patients to compare information obtained from wearable technologies (e.g., MIT E4 watch, actigraph accelerometer) and electronically captured patient-reported approaches (e.g., PROMIS® physical function item bank) with more traditional data sources such as clinician-based assessments (e.g., ECOG or Karnofsky performance status) and performance outcomes (e.g. 6 minute walk test or other PerfO). The research would analyze these data sources and their association with global anchor questions and other important clinical events such as hospitalizations, treatment changes, concomitant/supportive medication use and palliative procedures and survival.

Malignancy types where there are large expected changes in physical function during the course of the disease and its treatment, and multiple opportunities for functional assessment during clinical care are particularly well suited for study. Potential offerors should propose an oncology disease area, stage, clinical setting and endpoints, and select specific tools to analyze and compare data collected from wearables, ePRO questionnaires and clinician-reported outcomes. Focus should be applied to the sensitivity of various data sources to changes in physical function and identification of what a meaningful decrement and improvement for each physical function measure would be based on global anchoring questions and distributional methods.)

5.2.11 Test and validate computer models and tools on nonclinical data (e.g. data from in vitro and in vivo studies) to evaluate potential toxicity related to ENDS and other tobacco products or their constituents.

5.3 Computer Modeling and Simulation to Assess Product Risk

5.3.1 Develop new modeling approaches to assess the risk of new tobacco products that will potentially enter the market by considering how such products are likely to harm, or potentially harm users and non-users of the product based on factors including but not limited to exposure to toxicants, product characteristics and demographic attributes of the users and usage patterns.
5.3.2 Develop novel methods to model the carcinogenicity, genetic toxicity, and organ system toxicities resulting from chronic use of ENDS and other tobacco products and the contribution to adverse health conditions of a chemical mixture produced from a tobacco product by integrating diverse sources of available data – \textit{in silico}, \textit{in vitro}, \textit{in vivo}, and human clinical and epidemiology data.

5.3.3 Develop novel models for the demographics of a synthetic population in terms of probability distribution curves (normal distribution) based on:

a. Usage of ENDS and other tobacco products (including dual use)
b. Race
c. Gender
d. Age
e. Body Weight
f. Family structure and position within (e.g., child exposure to secondhand smoke in the home, car, or other locations)
g. Occupation and work premises (susceptibility to, or likelihood of a secondary ingestion, or secondary exposure such as secondhand smoke)
h. Establish tobacco product modeling validation requirements.

5.3.4 Develop novel methods to display model output in both graphical and numeric formats.

5.3.5 Develop novel quantitative risk assessment modeling methods that better capture total health risks of tobacco products. The new modeling methods should take into consideration all health risks of individual constituents as well as the ones associated with the whole mixture of chemical constituents produced from ENDS and other tobacco products. They should also address the wide heterogeneity that exists in health risk susceptibility and tobacco product use pattern of different human populations.

Modeling parameters may include, but are not limited to:

a. Type of tobacco product (e.g., cigarette, smokeless, e-cigarette) and dual use
b. Specifics of tobacco product (brand X Y or Z, top # based on market share, any other brands that data exist for in the database)
c. Group of chemicals or HPHCs (e.g., aldehydes, metals)
d. Concentration of chemicals in the smoke, aerosol or tobacco product (mean, range, etc.)
e. Tobacco product, intake rate – cigarettes smoked per day (e.g., 5, 10, 20, 40), volume of e-liquid used per day, smokeless product used per day (e.g., by mg, # of cans, # of “dips”)
f. Exposure frequency - How frequently a user is exposed (e.g., daily, one time per week, five days per month)
g. Exposure duration – How long a person has been using the tobacco product of interest (in years)
h. Body weight
i. Averaging time – Lifespan for a given population (differing population dynamics)
J. Smoking and ENDS use topography

5.3.6 Develop explainable modeling approaches to assess the impact of new tobacco products, policies, or regulations on tobacco use behaviors and the health of the U.S. population.
including the impacts on tobacco product initiation, cessation, switching, and dual use.

5.3.7 Develop and disseminate computational models and simulations that can be used as evidence for the safety and effectiveness of medical devices; establish medical device modeling validation requirements.

5.4 Collect and use patient input in regulatory decision-making

Patients are increasingly providing their input to spur patient-centric medical product development and to inform patient-centric regulation.

5.4.1 Develop and validate methods for collecting patient experience data.

5.4.2 Perform patient preference studies in preference sensitive areas for use in regulatory decision making (e.g. understanding benefit-risk tradeoffs, improving clinical trial designs, or prioritizing treatment outcomes).

5.4.3 Develop and validate patient-reported outcome measures (PROMs).

5.4.3.1 Perform "bridging" studies to adapt or update existing validated PROMs for new populations, indications, or situations (e.g. expanding from adult to pediatrics).

5.5 Human behavioral modeling to assess tobacco product use patterns to inform regulatory science

5.5.1 Develop behavioral modeling approaches that measure the impact of tobacco product quantity changes (i.e., increases, decreases) on youth, young adult, and adult tobacco use behaviors, including tobacco product initiation, cessation, switching, dual use, and frequency of use.

5.5.2 Using behavioral modeling approaches, measure the impact of tobacco product quantity changes (i.e., increases, decreases) on youth, young adult, and adult tobacco use behaviors, including tobacco product initiation, cessation, switching, dual use, and frequency of use.

5.6 Systems Modeling of the Opioid Crisis

FDA is seeking innovative systems modeling approaches to help understand the dynamics of the opioid crisis and the potential impact of interventions to address it. FDA is currently developing a model of the opioid crisis using system dynamics techniques as recommended by the National Academies of Sciences, Engineering, and Medicine (NASEM) in its 2017 report, Pain Management and the Opioid Epidemic. FDA is seeking complementary approaches to augment and support this model. These approaches may include:

• Complementary systems modeling and simulation modeling approaches, such as agent-based modeling, and economic modeling approaches. These models may support our understanding of the opioid crisis in general or specific complex features of the opioid crisis.

• Models of how opioid dependence, addiction, and opioid use disorder develop as a function of patient characteristics (e.g., medical conditions, socioeconomic background) and opioid use patterns (e.g., duration and frequency of use).

• Qualitative and quantitative models of prescribing decision making and behaviors: how
prescribers decide whether to treat acute and/or chronic pain with opioids, how they select a drug and dosing regimen, and how the introduction of new opioid products, including abuse-deterrent formulations, affects prescriber decision-making and behavior

6. Implement a New Prevention-Focused Food Safety System to Protect Public Health

The Food Safety Modernization Act (FSMA) mandates a new approach to FDA’s current food safety system by emphasizing prevention and risk-based priority setting and resource allocation to address the challenges of the modern food safety environment. Although prevention is paramount, enhanced response and investigation efforts to foodborne illness outbreaks when they occur, are also critical. To effectively implement this new food safety mandate, it is imperative that FDA ensure a strong science infrastructure that clearly identifies its research needs and collaborates with other public health and research agencies in the Federal government, state government agencies, academia, and private industry. Areas of interest include:

6.1 Establish and implement centralized planning and performance measurement processes:

6.1.1 Harmonize microbiological and chemical analytical methods development and validation across the OFVM Program to enhance detection and removal of unsafe contaminants from the Nation’s food and feed supply.

Note: Improved, validated rapid methods, with high levels of sensitivity and specificity, would enable FDA investigators and laboratories to quickly and accurately identify sources of contamination throughout the food supply chain, thereby protecting human and animal health. In addition, improved methods would also provide defensible data to show food products are free from harmful levels of microbial and chemical hazards. Research that gives FDA validated, practical and usable regulatory tools would benefit FDA in making regulatory decisions and providing guidance to industry.

6.2 Maintain mission critical science capabilities:

6.2.1 Identify emerging disciplines, sciences, and technologies to mitigate future risks in food safety.

Note: The primary focus is to advance research and development (R&D) into more rapid, sensitive and specific methods to detect, identify and quantify a variety of microbial and chemical hazards in foods (including dietary supplements) and animal feeds. Some of these methods can be expected to also enhance detection and protection against microbial and chemical hazards in cosmetics, which are also regulated by FDA.

7. Facilitate Development and Availability of Medical Countermeasures (MCMs) to Protect Against Threats to U.S. and Global Health and Security

FDA seeks to facilitate development of safe and effective MCMs through both intramural research and collaboration with external partners (e.g., academia, U.S. government agencies, non-governmental organizations, and industry). The FDA’s MCM regulatory science mission has a responsibility to develop the tools, standards, and approaches to assess medical safety, quality, and performance of MCMs. Furthermore, FDA is interested in advancing manufacturing innovations to ensure quality and integrity of MCM supply chain. Additional information on the FDA MCM initiative and projects is available at:
FDA will conduct a review for the potential of Dual Use as defined and in accordance with USG policy:

https://osp.od.nih.gov/biotechnology/dual-use-research-of-concern/

Areas of interest include:

**7.1 Develop, characterize, and qualify tools to support MCM development under the Animal Rule or Accelerated Approval Provisions**

7.1.1 Develop, evaluate and/or refine animal models for Chemical, Biological, and Radiological and Nuclear (CBRN) threat agents and emerging infectious diseases for the ability to demonstrate a response to the MCM that will be predictive for humans, including the ability to extrapolate pharmacokinetic/pharmacodynamic (PK/PD) data and/or immune correlates of protection to determine appropriate clinical dosing.

7.1.2 Develop and qualify *in silico* predictive models (e.g. microphysiological systems) and *in vitro* assays to complement the use of *in vivo* animal models to assess safety and efficacy of medical countermeasures.

7.1.3 Identify and qualify immune biomarkers for CBRN threat agents and emerging infectious diseases to enable comparisons to be made between animal model species and humans.

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391604.htm

7.1.4 Identify and qualify biomarkers that enhance the understanding of the mechanism of action of MCMs, and may provide measures of MCM product efficacy

7.1.5 Improve knowledge of natural history of pathophysiology of human diseases or conditions caused by CBRN threat agents and emerging infectious diseases to identify, qualify, and evaluate biomarkers

**7.2 Modernize tools to evaluate MCM product safety, efficacy, and quality; and improve/ensure MCM supply chain:**

7.2.1 Enhance FDA’s capabilities to collect, monitor, track, and analyze real-time and retrospective data associated with the use of public health emergency MCMs (e.g., develop and refine the capabilities necessary to use real world data for rapid assessment of the safety, efficacy and/or effectiveness of MCMs used for responses to potential or actual public health emergencies). Additional information on the FDA Monitoring and Assessment for Medical Countermeasures projects is available at:

https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm561377.htm

7.2.2 Identify and evaluate methods to improve the availability, performance, design, and reuse of personal protective equipment;

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5 *The “Animal Rule is defined under 21 CFR 314.600/21 CFR 601.90. Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses is defined under 21 CFR Part 601, Subpart E. Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses is defined under 21 CFR Part 314, Subpart H*
7.2.3 Develop reference materials (e.g. standardized challenge pools) related to relevant CBRN threat agents and emerging infectious diseases to facilitate development of preventive vaccines, therapeutics, and detection and diagnostic methods;

7.2.4 Refine/Improve existing or innovative technologies to improve the sensitivity, specificity, and robustness of testing methods used to measure MCM potency and in-process and final drug substance characteristics (for example, in-line sensors and process analytical technologies); and

7.2.5 Advance broadly-applicable, commercially-ready (MRL 4-6\(^6\)) tools, technologies, and platforms that improve manufacturing efficiency, consistency, and quality of MCMs to bolster the MCM supply chain; for example, “plug-and-play” modular unit operations applicable for downstream processing, or continuous manufacturing.

8. Strengthening Social and Behavioral Science at FDA by Enhancing Audience Understanding

FDA seeks to identify and improve science-based approaches, (tobacco products, foods, dietary supplements and cosmetics excluded) that enhance awareness, understanding, and informed decision-making by patients, consumers and health care professionals to promote health and reduce harms. There are six priority areas in which FDA seeks to enhance its communications. These areas are:

8.1 Assess awareness and understanding of FDA communications, especially among diverse audiences and populations, and identify methods to improve the comprehension of content, including numerical information

8.1.1 Identify effective ways to communicate so that patients and consumers, including those with low health literacy and limited English proficiency, are informed but not alarmed, assess knowledge and understanding of risk associated with use of FDA-approved products, assess the frequency and means of changing messages in order to promote continued attention to advice that is not new but remains important, evaluate methods to identify and accommodate cultural and language differences and assess the cost of these methods to the Government, and study the impact of different formats and amounts of numerical information in FDA communications for patients, health care providers, health educators and informal caregivers.

8.2 Explore ways that FDA communications can best complement those communicated by industry to enhance audience comprehension

8.2.1 Develop tools for measuring the effectiveness of messages that are being communicated to the public by industry advertisements and by FDA communications among patients and consumers, including those with low literacy and limited English proficiency

8.3 Assess public understanding of regulatory terms

\(^{6}\) Manufacturing Readiness Levels as defined by Department of Defense: [http://www.dodmrl.com/](http://www.dodmrl.com/)
8.3.1 Study the impact of FDA terms on the public's ability to comprehend FDA communications, and identify explanatory strategies or alternatives. Examples of FDA terms include: “safe and effective,” Over-The-Counter (OTC) monograph drugs, “voluntary recall,” and “product correction.”

8.4 Evaluate timing of release of recall or warning messages, how and when these messages can enhance impact, and how to communicate the end of a recall or warning.

8.4.1 Characterize how consumers, patients, and caregivers understand these messages; evaluate the ideal frequency and means of changing messages in order to promote continued attention to advice that is not new but remains important.

8.5 Studies to increase the safety of post-approval drug use

8.5.1 Develop innovative methods to create, facilitate and encourage research in the area of safe medication use that seeks to reduce preventable harm from drugs. Approaches could include the use of clinical studies, innovative messaging strategies, electronic health records, data mining, patient generated data, or mobile technologies, but this list is not exhaustive and innovative methods and approaches are encouraged. Sub areas of research interest include but are not limited to the following:

8.5.1.1 Develop and test novel dissemination methods that enhance FDA’s ability to target distribution of intervention materials to specific clinical practice audiences and/or patient populations.

8.5.1.2 Test safe use interventions that advance the field of implementation science within the healthcare system. Develop systems engineering approaches that could serve as a foundation to address multiple safe use issues.

8.5.1.3 Evaluate the capacity of big data analytics to empirically prioritize safe medication use issues within one or more health systems. Empiric prioritization could potentially complement expert-derived prioritization due to its speed, agility, and responsiveness to contextual factors within a health system.

8.5.1.4 Determine if new safe use management options might potentially be available for one or more identified medication safety risks as a result of the emerging precision medicine evidence base. Risks that have been probabilistically associated with medications through epidemiologic study in populations may be mediated by factors such as genetic polymorphisms in individuals. Knowledge of individual factors could guide therapeutic decisions and enhance safe use.

8.6 Studies to evaluate the safety of approved drug products

8.6.1 Improve the quality and effectiveness of Risk Evaluation and Mitigation Strategy (REMS) programs while minimizing program-related burden and access barriers.

8.6.1.1 Develop and evaluate new tools and approaches that can be integrated into the
healthcare system to prevent/mitigate the risks associated with approved drugs.

8.6.1.2 Develop and evaluate new visualization methods and approaches that can be integrated into the healthcare system to better understand and analyze safety data.

8.6.1.3 Develop and evaluate methods to assess REMS-related drug healthcare access barriers due to the implementation of REMS program.

8.6.1.4 Identify data sources and develop methods to evaluate REMS effectiveness and REMS related burden to healthcare providers and the healthcare system.

8.6.2 Use social and behavioral science methods in conjunction with large electronic healthcare data to enhance the understanding of factors (e.g. patient characteristics) that may influence the prescribers’ decisions to choose and switch between reference products and biosimilars or other biological or non-biological products within a class.

8.6.3 Develop and evaluate methods to enhance reporting, analysis, and prevention of medication errors. Approaches could include the use of electronic health records, predictive analytics, and techniques to determine the causes of errors and the effectiveness of regulatory actions to prevent errors.

9. Strengthening the Global Product Safety Net

Globalization has made FDA’s responsibilities increasingly challenging, affecting every type of product FDA regulates. The number of FDA-regulated shipments at 300 U.S. ports has more than doubled in the last 10 years. In 2006, approximately 15 million shipments of imported food and medical products crossed U.S. borders. In 2016, that number increased to 37 million. Additionally, more and more products come from developing countries where manufacturing systems may be less sophisticated and regulatory and manufacturing oversight may be minimal. As FDA continues to transform into a public health agency fully prepared for a complex, global regulatory environment, FDA seeks to improve its knowledge and capabilities to enhance its international operating model to advance global public health.

9.1. Advancing Global Public Health

9.1.1. Determine how to promote and assure implementation of the essential elements of a strong regulatory system in developing economies, including (a) determining core competencies for a regulatory workforce and components of a global regulatory workforce curriculum, (b) assessing other areas related to regulatory systems’ performance including conducting, costing, and financing analyses for regulatory systems, and (c) identifying and assessing existing regulatory strengthening evaluation tools utilized by governments and international organizations.

9.2. Analyzing and Utilizing Global Data to Manage Risks

9.2.1. Define analytical methods and tools to foster improved utilization of risk analytics
to inform strategies, priority-setting, and timely decision-making in the areas of inspections, training, regulatory cooperation and surveillance.

9.2.2. Develop predictive risk models that treat like risks in like ways across the supply chain regardless of the origin of the product.

9.2.3. Adopt new approaches to better aggregate and analyze multiple sources of information to fully identify risks and emerging trends based on comprehensive assessments of existing information platforms. The developed approach should include data mining of intelligence related sources (event reporting, testing results, alerts, customer complaints, news reports) to enable statistical analysis of correlations and threats. As an extension, integrate intelligence-based threat analysis into the risk-based allocation of inspection and testing resources.

9.2.4. Filter and analyze external indicators/signals/environmental vulnerabilities in the supply chain from various open-source intelligence and other sources to proactively identify the need for appropriate FDA interventions.

Note: Research in this area could include the development of informatics tools to connect multiple sources of information such as regulatory, economic, environmental, political and industrial factors to detectable risk signals and emerging risk trends. It could also include the development of data collection and analysis systems for external indicators/signals/environmental vulnerabilities in the supply chain from various sources intelligence and other media to alert FDA at early onset of the need for appropriate FDA actions or interventions.

Part II: Reporting Requirements and Deliverables

As part of the work to be performed under this BAA, the Contractor shall prepare and deliver the following reports throughout the period of performance. For all reports the Contractor shall submit electronic copies to the Contracting Officer (CO) and the Contracting Officers Representative (COR).

Reports:

1. Monthly Technical Progress Reports

On the fifteenth (15) day of each month for the previous calendar month, the contractor shall submit to the COR and the Contracting Officer a Technical Progress Report. Instructions for formulating Technical Progress Reports are detailed below. The Technical Progress Reports shall include project timelines and milestones summaries of product manufacturing, testing, and clinical evaluation. A Technical Progress Report will not be required for the period in which the Final Report is due. The Contractor shall submit two copies of the Technical Progress Report electronically via e-mail to the CO and COR. Any attachments to the e-mail report shall be submitted in Microsoft Word, Microsoft Excel, and/or Adobe Acrobat PDF files. Such reports shall include the following information:

   a. Title page containing: Technical Progress Report, the contract number and title, the period of performance or milestone being reported, the Contractor’s name, address, and other contact information, the author(s), and the date of submission;
b. Introduction/Background: An introduction covering the purpose and scope of the contract effort;

c. Progress: The report shall detail, document and summarize the results of work performed, test results, milestones achieved during the period covered and cumulative milestones achieved. Must also include a summary of work planned for the next two (2) reporting periods on a rolling basis;

d. Issues: Issues resolved, new issues and outstanding issues are enumerated with options and recommendation for resolution. An explanation of any difference between planned progress and actual progress, why the differences have occurred, and, if progress activity is delinquent, and what corrective steps are planned. Revised timelines are to be included.

e. Invoices: Summary of any invoices submitted during the reporting period.

f. Action Items: Summary table of activities or tasks to be accomplished by certain date and by whom.

g. Distribution list: A list of persons receiving the Technical Report

h. Attachments: Results on the project are provided as attachments

2. Final Report:

By the expiration date of the contract, the Contractor shall submit a 508 compliant Final Report that shall detail, document, and summarize the results of the entire contract work. The report shall explain comprehensively the results achieved. A draft Final Report will be submitted to the CO and COR for review and comments, then the Final Report original, copies, and an electronic file shall be submitted to the CO and COR for distribution to the Program office. Included in the final report shall be an executive summary (in plain language) within the report to summarize the results of the contract and include outcomes with possible impacts on FDA mission. The final report must have a table of contents and page numbers. Preferred Font: Calibri or Times New Roman and Size 11.

*Note: Some reports and other deliverables are relevant to specific activities that may or may not be performed during the contract period of performance. The Contractor, Contracting Officers Representative and Contracting Officer shall agree in the final contract negotiations on which reports and other deliverables are relevant and shall be required as deliverables as determined in the negotiated Statement of Work.

These reports are in addition to other reports and deliverables that may be required in the final negotiated SOW as referenced above.

3. Invoices: Cost and Personnel Reporting, and Variances from the Negotiated Budget:

While specific Invoice Procedures (based on contract type) will be stipulated in any resultant contract awarded from this announcement, for Cost Type Contracts, the Contractor shall be prepared to provide a detailed breakdown on invoices of the following cost categories:

a. Direct Labor - List individuals by name, title/position, hourly/annual rate, level of effort, and amount claimed.

b. Fringe Benefits - Cite rate and amount

c. Overhead - Cite rate and amount

d. Materials & Supplies - Include detailed breakdown when total amount is over $1,000.

e. Travel - Identify travelers, dates, destination, purpose of trip, and amount. List
separately, domestic travel, general scientific meeting travel, and foreign travel.
f. Consultant Fees - Identify individuals and amounts.
g. Subcontracts - Attach subcontractor invoice(s).
h. Equipment - Cite authorization and amount.
i. G&A - Cite rate and amount.
j. Total Cost
k. Fixed Fee (if applicable)
l. Total

The Contractor shall be held accountable for compliance with the stipulations stated in FAR 52.232-20 Limitation of Cost. Furthermore, invoices submitted under BAA awarded contracts must comply with the requirements set forth in FAR Clauses 52.232-25 (Prompt Payment) and 52.232-33 (Payment by Electronic Funds Transfer-System for Award Management) and/or applicable Far Clauses specified in the actual contract document.

Part III: Proposal Preparation and Submission

Section 1: The Application Process

The application process is in two (2) stages as follows:

Stage 1: Complete a cover page, Quad Chart, and White Paper in accordance with the preparation guidance below. Quad Charts and White Papers shall describe the effort in sufficient detail to allow evaluation of the concept's technical merit and its potential contribution to the FDA mission. Offerors whose Quad Chart and White Paper receive a favorable evaluation may be invited to submit a Full Proposal. Offerors whose Quad Chart and White Paper did not receive a favorable evaluation will be notified by email regarding technical deficiencies and/or lack of programmatic alignment.

Stage 2: If invited, Offeror will submit Full Proposals in accordance with the instructions provided in Section 5 below. Full Proposals will be evaluated against criteria as described in Part IV. Full Proposals that do not conform to the requirements outlined in the BAA or in the invitation will not be reviewed or considered for further action.

<table>
<thead>
<tr>
<th>Proposal Stage</th>
<th>Deadline for Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1: Quad Chart and White Paper</td>
<td>Anytime during open period</td>
</tr>
<tr>
<td>Stage 2: Full Proposal</td>
<td>Within 30 calendar days of Invitation (unless designated otherwise by the CO)</td>
</tr>
</tbody>
</table>

Section 2: Stage 1 Quad Chart and White Paper

Interested Offerors shall submit a White Paper which expands on the information provided in the Quad Chart. The initial submission is limited to a cover page, one-page Quad Chart (see attachment 3), White Paper not to exceed ten (10) pages, an addendum not to exceed two (2) pages and a Research and Development Justification not to exceed one (1) page, as discussed
below. If submissions exceed these limitations, only those pages previously defined will be reviewed. *Additionally, please know: “multiple white paper submissions on the same topic or closely related topics are discouraged.”*

**Combine all files and forms into a single searchable PDF file before submitting.**

**Quad Chart Format (One Page Limit):** All quad charts shall include the information indicated on the sample template located in **Attachment 3**.

1. Heading: Title, Research Area Addressed, Offeror point of contact, Company’s Name
2. Upper left: Objective, description of effort
3. Lower left: Benefits of proposed technology, challenges
4. Upper right: Picture or graphic
5. Lower Right: Milestones, cost, period of performance. White

**Paper Technical Information (Ten Page Limit):**

1. In general, the White Paper should provide a brief technical discussion of the Offeror’s objective, approach, level of effort, and the nature and extent of the anticipated results. Specifically, the White Paper shall include, at a minimum, the following core elements:
   a. brief discussion on how the proposed project aligns with the objectives of the FDA Advancing Regulatory Science Plan.
   b. a high-level Gantt chart showing an overview of the proposed activities and timelines.
   c. a brief description of the Offeror’s intellectual property ownership of the proposed project.
   d. an overview of the Offeror’s capabilities and experience (past and current) as they relate to the proposed program.
   e. An indication if this proposal should be directed to any specific Center(s) or office(s) for consideration

2. The cost portion of the White Paper shall contain a brief cost estimate revealing the component parts of the proposal and a breakdown of the total cost per year.

**Addendum (Two Page Limit):**

As an addendum to the White Paper, include overviews (two pages total) of the key personnel who will perform the research, highlighting some of their qualifications and experience.

3. Justification for Research and Development (One Page Limit):

Offerors shall submit, with the white paper package, a one (1) page justification describing how the Offeror’s project falls under the FAR definition of Research and Development (See attachment 4 for details).

Restrictive markings on White Papers: Proposal submissions will be protected from unauthorized disclosure in accordance with FAR Subpart 15.207, applicable law and HHS regulations. Offeror’s that include in their proposal, data that they do not want disclosed, shall mark their proposal in accordance with the instructions contained FAR 52.215-1(e) ‘Restrictions on
disclosure and use of data.’

Mark the title page with the following legend:

This proposal includes data that shall not be disclosed outside the Government and shall not be duplicated, used, or disclosed—in whole or in part—for any purpose other than to evaluate this proposal. If, however, a contract is awarded to this offeror as a result of—or in connection with—the submission of this data, the Government shall have the right to duplicate, use, or disclose the data to the extent provided in the resulting contract. This restriction does not limit the Government’s right to use information contained in this data if it is obtained from another source without restriction. The data subject to this restriction are contained in sheets [insert numbers or other identification of sheets]; and

Section 3: Quad Chart and White Paper Submission

Quad Charts and White Papers shall be emailed directly to the following email address: FDABAA@fda.hhs.gov.

Include “Research Area #_ FDABAA-19-00123-A3 WHITE PAPER” in the email subject line. Offerors must select a primary research area to submit the white paper under even if the submission qualifies for multiple research areas. White Papers must be submitted in the following format but do not require any special forms:

• Single PDF formatted file as an email attachment
• Page Size: 8 ½ x 11 inches
• Page limit: 10 pages
• Margins – 1 inch
• Spacing – single
• Font – Arial, 12-point

The file shall not exceed 2 Megabytes of storage space. Movie and sound file attachments, URL Links, or other additional files, will not be accepted.

Classification: All Quad Chart and White Paper submissions must be UNCLASSIFIED.

Notification to Offerors: All Offerors will receive an email acknowledging receipt of their Quad Chart and White Paper submission. Debriefings for Quad Chart and White Paper will not be provided; however, feedback may be provided in the response letter from FDA.

IMPORTANT NOTE: Titles given to the White Papers and Full Proposals should be descriptive of the work proposed and not be merely a copy of the title of this solicitation. As an iteration, “multiple white paper submissions on the same topic or closely related topics are discouraged.”

Section 4: Stage 2 Full Proposal Preparation

With a successful review of the Offeror’s White Paper, the Offeror may be invited to submit a Full Proposal. The Full Proposal must be prepared as two separate volumes as follows: Volume I Technical Proposal and Technical Proposal Appendices; Volume II Cost Proposal and Cost Proposal Appendices.
A. Volume I - Technical Proposal

The technical proposal page limit is 50 pages (page limitation for items 4 thru 8) of technical volume, including figures, tables and graphs unless otherwise specified by the Contracting Officer. If the proposal exceeds the number of pages specified, only the pages up to the limit will be reviewed. A page is defined as 8.5 X 11 inches, single-spaced, with one-inch margins in type no smaller than 12-point font.

1. Cover Page: This should include the words “Full Technical Proposal” and the following:
   - BAA number
   - Title of proposal
   - Identity of prime Offeror and complete list of subcontractors, if applicable
   - Technical contact (name, address, phone/fax, electronic mail address)
   - Administrative/business contact (name, address, phone/fax, electronic mail address)
   - Duration of effort

2. Official Transmittal Letter. This is an official transmittal letter with authorizing official signature.

3. Table of contents: an alphabetical/numerical listing of the sections within the proposal, including corresponding page numbers.

4. Executive Summary

5. Introduction – Overview of the project.

6. Statement of Work: The SOW should clearly detail the scope and objectives of the effort and the technical approach. For proposals exceeding 12 months in length, the Offeror shall identify if the proposed effort constitutes a single, indivisible undertaking, or if the work can be separated into severable deliverables that meet a need of the Government. If the proposal can be separated into severable deliverables, the Offeror shall identify these points of severability in their SOW. It is anticipated that the proposed SOW will be incorporated as an attachment to the resultant award instrument. To that end, the proposal must include a severable, self-standing SOW, without any proprietary restrictions which can be attached to the contract award (preferably provided in MSWord). The SOW must be organized by task and subtask with a detailed description of the work that will occur in each task. Tasks should have a deliverable or deliverables associated to them. Offerors must include in the SOW, standards for assessing the acceptability of any proposed deliverable.

7. Gantt Chart, Work Breakdown Structure and Milestones: A detailed Gantt Chart with associated Work Breakdown Structure (WBS) (Level 3) and program Milestones must be provided as part of the technical submission.

8. Deliverable Schedule: A detailed description of the results and products to be delivered inclusive of the timeframe in which they will be delivered. Specific due dates for deliverables must be established at the time of award. If applicable, Offerors shall clearly identify points of severability in their proposed deliverable schedule.

9. Security Planning: The work to be performed under this contract may involve access to sensitive program information. Therefore, the Offeror shall develop and submit a written Draft Security Plan that describes their procedures and policies to defend against theft, tampering, or destruction of product-related material, equipment, documents, information, and data. The Offeror is invited to submit a request for waiver if he or she believes the proposed work is exempt from some or all of the security requirements or if the Offeror can demonstrate that commensurate protective measures have been applied that afford an equal level of protection. Requests for waivers should be submitted to the
Contracting Officer.

10. Intellectual Property: For issued patents or published patent applications that will be used in the performance of the contract, provide the patent number or patent application publication number, a summary of the patent or invention title, and indicate whether the Offeror is the patent or invention owner.

11. Biographical Sketches: This Section shall contain the biographical sketches for only the key personnel from both the contractor and subcontractor(s): The Full Proposal must list the names and proposed duties of the professional personnel, consultants, and key subcontractor employees assigned to the project. Resumes shall be included in the appendices in Volume I of the Full Proposal. The resumes should contain information on education, background, recent experience, and specific or technical accomplishments as they pertain to their ability to support the objectives of this project.

12. The Offeror shall provide a list of the last three (3) government related contracts during the past three (3) years and all contracts currently being performed that are similar in nature to the BAA scope. Contracts listed may include those entered into by the Federal Government, agencies of state and local governments and commercial concerns. Offerors may also submit past performance information regarding predecessor companies, key personnel who have relevant experience or subcontractors that will perform major or critical aspects of the requirement when such information is relevant to the proposed project. For the purposes of this BAA, a "major subcontract" is defined as a subcontract that exceeds $25,000.

Include the following information for each contract or subcontract listed:

1. Name of Contracting Organization
2. Contract Number (for subcontracts, provide the prime contract number and the subcontract number)
3. Contract Type
4. Total Contract Value
5. Description of Requirement
6. Contracting Officer's Name and Telephone Number
7. Program Manager's Name and Telephone Number

The Offeror may provide information on problems encountered on the identified contracts and the Offeror's corrective actions.

B. Volume I – Appendices

Appendices to Volume I shall contain supplemental data that shall accompany the technical proposal. The combined page total of Appendices in Volume I is 20 pages unless specified otherwise in the full proposal invitation letter. Additional specific information to be included is referenced below. If a particular item is not relevant to the proposed effort, state that it is not applicable along with any supporting justification.

<table>
<thead>
<tr>
<th>Item</th>
<th>Required</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated Quad Chart</td>
<td>Yes</td>
<td>Attachment 3</td>
</tr>
</tbody>
</table>
2 Protection of Human Subjects
   If Applicable, Offerors must submit confirmation of an Office for Human Research Protections (OHRP) Approved Federal-wide Assurance (FWA) as well as Approved Institutional Review Board (IRB) with proposal. Please note, the Prime contractor in any partnership must have an approved FWA and cannot rely upon the subcontractor’s FWA. http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf
   See Section F below for additional details.

3 Animal Use
   If Applicable See Section G below.

4 Intellectual Property
   Yes

5 Biographical Sketches
   Yes

6 Use of Select Agents
   If Applicable http://www.cdc.gov/od/sap
   USDA Select Agent and Toxin List
   USDA Select Agent Services

7 Laboratory License Requirements
   If Applicable

8 Security
   If Applicable

C. Volume II – Cost Proposal

The cost proposal shall contain sufficient information for meaningful cost evaluation, and should not exceed 20 pages not including subcontractor proposals unless specified otherwise in the full proposal invitation letter. Additionally, a cost summary (not to exceed 2 pages) shall be prepared and submitted in conjunction with the detailed cost proposal. The detailed costs must readily track back to the cost presented in the summary and the WBS in the associated Project Gantt Chart. The Offeror must also provide a narrative to support the requirements in each cost element. The cost breakdown by tasks should use the same task numbering as the WBS in the Technical Proposal SOW. Options should be priced separately.

• Proposal Cover Sheet: The following information shall be provided on the first page of your pricing
1. BAA Number;
2. Title of proposal;
3. Topical Area;
4. Name and address of Offeror;
5. Name and telephone number of the primary point of contact;
6. Name, address, and telephone number of Contract Administration Office, (if available);
7. Name, address, and telephone number of Audit Office (if available);
8. Proposed cost and/or price, profit or fee (as applicable) and total cost;
9. The following statement: By submitting this proposal, the Offeror, if selected for discussions, grants the Contracting Officer or an authorized representative the right to request and examine, at any time before award, any of those books, records, documents and/or other records directly pertinent to the information requested or submitted.
10. Date of submission;
11. Name, title and signature of authorized representative; and
12. DUNS number
13. Desired Contract Type and justification for why.

- Basic Cost/Price Information: The cost proposal shall contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the line items of the proposed cost or price. The following cost elements shall be included by milestone, event or calendar year as applicable:

i. Direct Labor- Individual labor category or person, with associated labor hours and unburdened direct labor rates;

ii. Indirect Costs – Fringe Benefits, Overhead, G&A, etc. (Must show base amount and rate and include audited rate agreements if available); The offeror shall also provide the name and POC for the cognizant agency that established the rate agreement.

iii. Travel – Separated by destinations and include number of trips, durations-number of days, number of travelers, per diem (hotel and meals in accordance with the Federal Travel Regulations,), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc;

iv. Subcontract – A cost proposal shall be submitted by the subcontractor. The subcontractor’s cost proposal shall include, on company letterhead, the complete company name and mailing address, technical and administrative/business points of contact, email address, and telephone number. Include the DUNS number. If the subcontractor’s work entails any unpredictable aspects (e.g. includes experimentation, process development, etc.) a cost proposal conforming to all requirements of this section (4.C.) shall be provided, and shall reference the WBS of the prime contractor’s proposal. If the subcontractor/vendor is providing commercially available, routine services/products (e.g. facilities audits; manufacturing from a defined protocol; off-the-shelf reagents, hardware, or software; etc.) then a less detailed price quote is allowable. In each case where the latter level of detail is provided, the Offeror shall assign subcontractor/vendor costs to the WBS, and shall be prepared to document multiple competitive quotes for the service/product.

v. Consultant – Provide consultant agreement or other document which verifies the proposed loaded hourly rate and labor category;

vi. Materials shall be specifically itemized with costs or estimated costs. Where possible, indicate pricing method (e.g., competition, historical costs, market survey, etc.). Include supporting documentation, i.e. vendor quotes, catalog price lists and past invoices of similar purchases,

vii. Other Direct Costs, especially any proposed items of equipment.
Equipment generally must be furnished by the Offeror. Justifications must be provided when Government funding for such items is sought.

viii. Fee/profit including percentages.

ix. Certified Cost and Pricing data shall be provided for proposals over $750,000.00 (FAR 15.403-4(a)(1)).

D Volume II – Cost Proposal Appendices

Appendices to Volume II contain supplemental data of a cost and non-cost nature that should accompany the cost proposal. The combined total of Volume II appendices should not exceed 20 pages unless specified otherwise in the full proposal invitation letter. Additional specific information to be included is referenced below. If a particular item in not relevant to the proposed effort, state that it is not applicable along with any supporting justification.

<table>
<thead>
<tr>
<th>Item</th>
<th>Required</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DUNS, TIN and NAICS</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2 Representation and Certifications</td>
<td>Yes</td>
<td>FAR 4.1201</td>
</tr>
<tr>
<td>3 HHS Small Business Subcontracting Plan</td>
<td>If Applicable (over $700,000.00 and not a small business)</td>
<td>Template Provided as Separate Attachment to Announcement</td>
</tr>
<tr>
<td>4 Summary of Related Activities</td>
<td>Yes</td>
<td>Attachment 1</td>
</tr>
<tr>
<td>5 Disclosure of Lobbying Activities</td>
<td>If Applicable</td>
<td>FAR 52.203-11</td>
</tr>
</tbody>
</table>

E. Representation and Certifications:

Prospective contractors shall complete electronic annual representations and certifications at SAM accessed via [https://www.sam.gov/portal/SAM/#1](https://www.sam.gov/portal/SAM/#1) as a part of required registration (see FAR 4.1102). Prospective contractors shall update the representations and certifications submitted to SAM as necessary, but at least annually, to ensure they are kept current, accurate, and complete. The representations and certifications are effective until one year from date of submission or update to SAM.
F. Studies That Involve Human Subjects

All research under this BAA must address the involvement of human subjects and protections from research risk related to their participation in the proposed research plan and comply with 32 CFR 219, 10 U.S.C. 980, and, as applicable, 21 CFR Parts 11, 50, 54, 56, 312) (45 CFR Part 46) and the ICH as well as other applicable federal and state regulations. HHS Policy also requires that women and members of minority groups and their subpopulations: children and the elderly (pediatric and geriatric) must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification is provided with respect to the health of the subjects or the purpose of the research. The HHS policy on studies that involved human subjects can be accessible through the HHS website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

Research Projects involving humans and/or human specimens can only be initiated with written approval by the FDA Contracting Officer.

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 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 (“applicable trials”) for inclusion in the ClinicalTrials.gov database. More detailed information on the definition of “applicable clinical trial” and the registry and results reporting requirements can be found at https://clinicaltrials.gov/ct2/manage-recs/fdaaa.

FDAAA also added new requirements concerning clinical trials supported by grants and contracts from HHS, including FDA. Under these provisions, any contract or progress report forms required under a contract from any part of HHS, including FDA, must include a certification that the “responsible party” has submitted all required information to the ClinicalTrials.gov registry database. The responsible party is the term used in Title VIII of FDAAA (PL 110-85) to refer the entity or individual responsible for meeting FDAAA’s requirement. Under BAA contracts, the awardee assumes the responsibility, and will register a clinical investigation and submit Clinical Trial Information to the Clinical Trial Registry Data Bank if determined to be an applicable clinical trial. In case where the existing policy at the contractor’s institution requires a registration at the Clinical Trial Registry, the contractor shall provide a letter that clearly states the policy and the extent of responsibility within 30 days of the Award/Contract. This letter should be signed by the contractor and cosigned by the institutional official, and sent to the COR and the contracting officer (CO). More detailed information on the definition of ”applicable clinical trial" and the “responsible party” can be found at http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf.

There are also provisions regarding when agencies within HHS, including FDA, are required to verify compliance with the database requirements before releasing funding to contractors. Specifically:

352.270-4a Notice to Offerors, Protection of Human Subjects (DEC 2015)

These regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of human subjects participating in research activities supported or conducted by HHS.

(b) The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data or identifiable public information through intervention or interaction with the individual, or identifiable private information. In most cases, the regulations extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. 45 CFR part 46 does not directly regulate the use of autopsy materials; instead, applicable state and local laws govern their use.

(c) Activities which involve human subjects in one or more of the categories set forth in 45 CFR 46.101(b)(1)-(6) are exempt from complying with 45 CFR part 46. See http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

(d) Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal.

(e) In accordance with 45 CFR part 46, offerors considered for award shall file an acceptable Federal-wide Assurance (FWA) of compliance with OHRP specifying review procedures and assigning responsibilities for the protection of human subjects. The FWA is the only type of assurance that OHRP accepts or approves. The initial and continuing review of a research project by an institutional review board shall ensure that: the risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result; selection of subjects is equitable; and informed consent will be obtained and documented by methods that are adequate and appropriate. Depending on the nature of the research, additional requirements may apply; see http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.111 for additional requirements regarding initial and continuing review. HHS regulations for the protection of human subjects (45 CFR part 46), information regarding OHRP registration and assurance requirements/processes, and OHRP contact information is available at the OHRP website (at http://www.hhs.gov/ohrp/assurances/index.html).

(f) Offerors may consult with OHRP only for general advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects. ONLY the contracting officer may offer information concerning a solicitation.

(g) The offeror shall document in its proposal the approved FWA from OHRP, related to the designated Institutional Review Board (IRB) reviewing and overseeing the research. If the offeror does not have an approved FWA from OHRP, the offeror must obtain an FWA before the deadline for proposal submission. When possible, the offeror shall also certify the IRB’s review and approval of the research. If the offeror cannot obtain this certification by the time of proposal submission they must include an explanation in their proposal. Never conduct research covered by 45 CFR part 46 prior to receiving certification of the research’s review and approval by the IRB.

352.270-4b Protection of Human Subjects (DEC 2015)

(a) The Contractor agrees that the rights and welfare of human subjects involved in research under this contract shall be protected in accordance with 45 CFR part 46 and with the Contractor’s current Federal-wide Assurance (FWA) on file with the Office for Human Research Protections (OHRP), Department of Health and Human Services. The Contractor further agrees to provide certification at least annually that the Institutional Review Board has reviewed and approved the procedures, which involve human subjects in accordance with 45 CFR part 46 and the Assurance of Compliance.

(b) The Contractor shall bear full responsibility for the performance of all work and services
involving the use of human subjects under this contract and shall ensure that work is conducted in a proper manner and as safely as is feasible. The parties hereto agree that the Contractor retains the right to control and direct the performance of all work under this contract. Nothing in this contract shall create an agency or employee relationship between the Government and the Contractor, or any subcontractor, agent or employee of the Contractor, or any other person, organization, institution, or group of any kind whatsoever. The Contractor agrees that it has entered into this contract and will discharge its obligations, duties, and undertakings and the work pursuant thereto, whether requiring professional judgment or otherwise, as an independent Contractor without creating liability on the part of the Government for the acts of the Contractor or its employees.

(c) Contractors involving other agencies or institutions in activities considered to be engaged in research involving human subjects must ensure that such other agencies or institutions obtain their own FWA if they are routinely engaged in research involving human subjects or ensure that such agencies or institutions are covered by the Contractors’ FWA via designation as agents of the institution or via individual investigator agreements (see OHRP website at: http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf - PDF).

(d) If at any time during the performance of this contract the Contractor is not in compliance with any of the requirements and or standards stated in paragraphs (a) and (b) above, the Contracting Officer may immediately suspend, in whole or in part, work and further payments under this contract until the Contractor corrects the noncompliance. The Contracting Officer may communicate the notice of suspension by telephone with confirmation in writing. If the Contractor fails to complete corrective action within the period of time designated in the Contracting Officer’s written notice of suspension, the Contracting Officer may, after consultation with OHRP, terminate this contract in whole or in part.

352.270-10 Notice to Offerors – Protection of Human Subjects, Research Involving Human Subjects Committee (RIHSC) Approval of Research Protocols Required (DEC 2015)

(a) All Offerors proposing research expected to involve human subjects shall comply with the regulations set forth in 45 CFR Part 46, and with the provisions at HHSAR 352.270-4a.

(b) The Offeror shall have an acceptable Assurance of Compliance on file with the Office for Human Research Protections (OHRP), whenever it submits a proposal to the FDA for research expected to involve human subjects. Direct questions regarding Federal-wide Assurance to OHRP. The Offeror’s proposal shall include a copy of the acceptable Assurance of Compliance.

(c) After the contract has been awarded, the Contractor shall take the following actions:

(1) The Institutional Review Board (IRB) specified in the Offeror’s Assurance of Compliance, hereafter referred to as “the local IRB,” shall review the proposed research protocol. A letter from the local IRB stating that the proposed research protocol has been reviewed and approved, and thus adequately protects the rights and welfare of human subjects involved, or a letter stating that the proposed research is exempt under 45 CFR 46.101(b) shall be submitted to the Contracting Officer.

(2) Upon award, the successful Offeror, hereafter “the Contractor,” shall submit its proposed research protocol to the FDA’s Research Involving Human Subjects Committee (RIHSC). The RIHSC or its designee will review and approve the research protocol to assure it adequately protects the rights and welfare of human subjects involved. The RIHSC or designee will also determine whether the proposed research is exempt under 45 CFR 46.101(b). The Contractor shall submit, to the Contracting Officer of record, a copy of the RIHSC’s or its designee’s letter stating that it reviewed and approved the proposed research protocol.
(d) The Contractor shall not advertise for, recruit, or enroll human subjects, or otherwise commence any research involving human subjects until RIHSC or its designee reviews and approves its research. The Contractor may begin other limited aspects of contract performance prior to receiving RIHSC’s or designee’s approval of the proposed research protocol. Research involving human subjects may commence immediately upon the Contractor’s receipt of RIHSC’s or designee’s approval; however, the Contractor shall submit a copy of RIHSC’s or its designee’s approval to the Contracting Officer within three business days of its receipt.

(e) A Contractor’s failure to obtain RIHSC’s or its designee’s approval of its proposed research may result in termination of its contract. However, failure to obtain RIHSC’s or its designee’s approval during initial review will not automatically result in termination of the contract. Instead, the Contractor may correct any deficiencies identified during the initial RIHSC or designee review and resubmit the proposed research protocol to RIHSC or its designee for a second review. The Contractor is encouraged to solicit the RIHSC’s or its designee’s input during the resubmission process.

(f) The Contractor shall seek RIHSC’s or its designee’s and local IRB review and approval whenever making modifications, amendments or other changes to the research protocol. Such modifications, amendments and changes include, but are not limited to changes in investigators, informed consent forms, and recruitment advertisements. The Contractor may institute changes immediately after receiving both the local IRB and RIHSC or its designee approval (except when necessary to eliminate apparent immediate hazards to the subject); however, the Contractor shall submit a copy of the letter evidencing RIHSC’s or its designee’s approval of the proposed changes to the Contracting Officer within three business days of its receipt.

352.270-13 Continued Ban on Funding Abortion and Continued Ban on Funding of Human Embryo Research (DEC 2015)

(a) The Contractor shall not use any funds obligated under this contract for any abortion.

(b) The Contractor shall not use any funds obligated under this contract for the following:

(1) The creation of a human embryo or embryos for research purposes; or

(2) Research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury of death greater than that allowed for research on fetuses in utero under 45 CFR Part 46 and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

(c) The term “human embryo or embryos” includes any organism, not protected as a human subject under 45 CFR Part 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes of human diploid cells.

(d) The Contractor shall not use any Federal funds for the cloning of human beings.

352.211-3 Paperwork Reduction Act (DEC 2015)

(a) This contract involves a requirement to collect or record information calling either for answers to identical questions from 10 or more persons other than Federal employees, or information from Federal employees which is outside the scope of their employment, for use by the Federal government or disclosure to third parties; therefore, the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.) shall apply to this contract. No plan, questionnaire, interview guide or other similar device for collecting information (whether repetitive or single time) may be used without the Office of Management and Budget (OMB) first providing clearance. Contractors and the Contracting Officer’s Representative shall be guided by the provisions of 5 CFR part 1320, Controlling Paperwork Burdens on the Public, and seek the advice of the HHS operating division or Office of the Secretary Reports Clearance Officer to determine the procedures for acquiring OMB clearance.
(b) The Contractor shall not expend any funds or begin any data collection until the Contracting Officer provides the Contractor with written notification authorizing the expenditure of funds and the collection of data. The Contractor shall allow at least 120 days for OMB clearance. The Contracting Officer will consider excessive delays caused by the Government which arise out of causes beyond the control and without the fault or negligence of the Contractor in accordance with the Excusable Delays or Default clause of this contract.

G. Animal Welfare

If the Offeror proposes to use contract funds to conduct animal studies, the Offeror must comply with the following provision:

352.270-5a Notice to Offerors of Requirement for Compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals (DEC 2015)

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy) establishes a number of requirements for research activities involving animals. Before awarding a contract to an offeror, the organization shall file, with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), a written Animal Welfare Assurance (Assurance) which commits the organization to comply with the provisions of the PHS Policy, the Animal Welfare Act, and the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC). In accordance with the PHS Policy, offerors must establish an Institutional Animal Care and Use Committee (IACUC), qualified through the experience and expertise of its members, to oversee the institution’s animal program, facilities, and procedures. Offerors must provide verification of IACUC approval prior to receiving an award involving live vertebrate animals. No award involving the use of animals shall be made unless OLAW approves the Assurance and verification of IACUC approval for the proposed animal activities has been provided to the Contracting Officer. Prior to award, the Contracting Officer will notify Contractor(s) selected for projects involving live vertebrate animals of the Assurance and verification of IACUC approval requirement. The Contracting Officer will request that OLAW negotiate an acceptable Assurance with those Contractor(s) and request verification of IACUC approval. For further information, contact OLAW at NIH, 6705 Rockledge Drive, RKL1, Suite 360, MSC 7982 Bethesda, Maryland 20892-7982 (E-mail: olaw@od.nih.gov; Phone: 301–496–7163).

In addition, the Offeror must demonstrate its understanding and ability to comply with the Public Health Services (PHS) Policy on Humane Care and Use of Laboratory Animals http://grants.nih.gov/grants/olaw/olaw.htm If the Offeror has an Animal Welfare Assurance on file with the Office of Extramural Research (OER), Office of Laboratory Animal Welfare (OLAW), provide the Assurance number with the proposal. If the Offeror proposes animal studies, the Offeror must submit a plan that describes how the Offeror will comply with the PHS Policy and addresses the five points listed below:

a. Provide a detailed description of the proposed use of the animals in the work outlined in the experimental design and methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
b. Justification of the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and their numbers.
c. Provide information on the veterinary care of the animals involved.
d. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable
restraining devices where appropriate to minimize comfort, distress, pain, and injury.
e. Describe any euthanasia method to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association (http://www.avma.org/resources/euthanasia.pdf). If not, present a justification for not following the recommendations.

H. Prohibition on the Use of Appropriated Funds for Lobbying Activities HHSAR 352.270-10 Anti-Lobbying (Jan 2006):

The contractor is hereby notified of the restrictions on the use of Department of Health and Human Services’s funding for lobbying of Federal, State and Local legislative bodies.

Section 1352 of Title 31, United Stated Code (Public Law 101-121, effective 12/23/89), among other things, prohibits a recipient (and their subcontractors) of a Federal contract, grant, loan, or cooperative agreement from using appropriated funds (other than profits from a federal contract) to pay any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with any of the following covered Federal actions; the awarding of any Federal contract; the making of any Federal grant; the making of any Federal loan; the entering into of any cooperative agreement; or the modification of any Federal contract, grant, loan, or cooperative agreement. For additional information of prohibitions against lobbying activities, see FAR Subpart 3.8 and FAR Clause 52.203-12.

In addition, the current Department of Health and Human Services Appropriations Act provides that no part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support, or defeat legislation pending before the Congress, or any State or Local legislative body except in presentation to the Congress, or any State or Local legislative body itself as stated in P.L. 109-149, Title V, section 503(a), as directed by P.L. 110-5, Div. B, Title I, section 104.

The current Department of Health and Human Services Appropriations Act also provides that no part of any appropriation contained in this Act shall be used to pay the salary or expenses of any contract or grant recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress, or any State or Local legislature as stated in P.L. 109-149, Title V, section 503(b), as directed by P.L. 110-5, Div. B, Title I, section 104.

I. Use of Select Agent

An HHS chaired committee of contracting, security, safety and scientific program management will assess the applicability of the facilities, regulations, policies, and procedures for meeting the U.S. requirements described in 42 CFR part 73, 7 CFR part 331, and/or 9 CFR part 121.

J. Laboratory License Requirements

The Contractor shall comply with all applicable requirements of Section 353 of the Public Health Service Act (Clinical Laboratory Improvement Act as amended). This requirement shall also be included in any subcontract for services under the contract.

K. Data Rights Clause

All contracts awarded as a result of this BAA shall be subject to FAR 52.227-14 Rights in Data –
General and any other data rights clause that the FDA deems necessary for the work being conducted.

L. Advanced Understandings

1. Publications: 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.

Any manuscript or scientific meeting abstract containing data generated under this contract must be submitted for FDA Project Officer review no less than thirty (30) calendar days for manuscripts and fifteen (15) calendar days for abstracts before submission for public presentation or publication. Contract support shall be acknowledged in all such publications. A "publication" is defined as an issue of printed material offered for distribution or any communication or oral presentation of information.

2. Press Releases: The Contractor agrees to accurately and factually represent the work conducted under this contract in all press releases. Misrepresenting contract results or releasing information that is injurious to the integrity of FDA may be construed as improper conduct. Press releases shall be considered to include the public release of information to any medium, excluding peer-reviewed scientific publications. The Contractor shall ensure that the Project Officer has received an advance copy of any press release related to this contract not less than four (4) working days prior to the issuance of the press release.

3. Export control notification: Offerors are responsible for ensuring compliance with all export control laws and regulations that maybe applicable to the export of and foreign access to their proposed technologies. Offerors may consult with the Department of State with any questions regarding the International Traffic in Arms Regulation (ITAR) (22 CRF Parts 120-130) and/or the Department of Commerce regarding the Export Administration Regulations (15 CRF Parts 730-774).

4. Manufacturing Standards: The Good Manufacturing Practice Regulations (GMP)(21 CFR Parts 210-211) and regulations pertaining to biological products (21 CFR Part 600) and regulations pertaining to diagnostic products (21 CFR Part 860) will be the standard to be applied for manufacturing, processing, packaging, storage and delivery of this product.

**Note:** If at any time during the life of the contract, the Contractor fails to comply with GMP in the manufacturing, processing, packaging, storage, stability and other testing of the manufactured drug substance or product and delivery of this product and such failure results in a material adverse effect on the safety, purity or potency of the product (a material failure) as identified by the FDA, the Offeror shall have thirty (30) calendar days from the time such material failure is identified to cure such material failure. If the Offeror fails to take such an action to the satisfaction of FDA Project Officer within the thirty (30) calendar day period, then the contract may be terminated.

5. Prohibition on contractor Involvement with Terrorist Activities: The Contractor acknowledges
that U.S. Executive Orders and Laws, including but not limited to Executive Order 13224 and Public Law 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

6. Subcontracting Plans: Successful contract proposals that exceed $700,000, submitted by all but small business concerns, will be required to submit a Small Business Subcontracting Plan in accordance with FAR 52.219-9.

7. Identification and Disposition of Data: the Contractor shall be required to provide certain data generated under this contract to the FDA. FDA reserves the right to review any other data determined by FDA to be relevant to this contract. The contractor shall keep copies of all data required by the FDA relevant to this contract for the time specified by the FDA.

8. Confidentiality of Information: The following information is covered by HHSAR Clause 352.224-70, Privacy Act (DEC 2015): Data obtained from human subjects.

Section 5: Full Proposal Submission

Full Proposals must be emailed to FDABAA@FDA.HHS.GOV by the date specified in the invitation letter. If the Full Proposal attachments exceed the size limitation for email the Offeror shall contact the contracting officer to arrange for other delivery methods.

Offerors shall include in the Full Proposal Cover Sheet:

- The name, title, mailing address, telephone number, and fax number of the company or organization;
- The name, title, mailing address, telephone number, fax number, and e-mail address of the division point of contact regarding decisions made with respect to the Offeror and who can obligate the proposal contractually;
- The name, title, mailing address, telephone number, fax number, and e-mail address and those individual(s) authorized to negotiate with the USG; and
- A statement indicating you are submitting a Full Proposal for consideration.

*Note: Each volume of the proposal must be submitted as a separate and searchable Portable Document File (PDF) compatible with Adobe Acrobat version 7.0 or earlier.

Withdrawal of Proposals:

1. A proposal may be withdrawn by written notice received at any time prior to contract award. Withdrawals are effective upon receipt of notice by the Contracting Officer via email.

2. The government may reject Full Proposal submissions that are deemed non-compliant, i.e., that significantly deviate from the instructions in the Broad Agency Announcement or invitation to submit a full proposal.

Information to be requested from Successful Offerors: Offerors whose proposals are selected for potential award will be contacted to provide additional administrative information if required for award. Such information may include explanations and other information applicable to the
Offerors that are not responsive in a timely manner to Government requests for information (defined as meeting Government deadlines established and communicated with the request) may be removed from award consideration. Offerors that request significant revisions to their proposal subsequent to their selection for potential award may be removed from award consideration. Offerors may also be removed from award consideration if the Offeror and the Government fail to negotiate mutually agreeable terms within a reasonable period of time.

All proposals are treated as privileged information prior to award and the contents are disclosed only for the purpose of evaluation. The Offeror must indicate any limitation to be placed on disclosure of information contained in the proposal.

Section 6: General Information

PRELIMINARY INQUIRIES: FDA realizes that the preparation of a research proposal often represents a substantial investment of time and effort by the Offeror. Therefore, in an attempt to minimize this burden, FDA encourages organizations and individuals interested in submitting research proposals to make preliminary inquiries as to the general need for the type of research effort contemplated before expending extensive effort in preparing a detailed research proposal or submitting proprietary information. The email inquiries should specify one of the subtopics from the "Research Areas of Interest" section in the subject line and shall contain one or two paragraphs on the Offeror's approach, the project goals and the approximate amount of funding needed for the project. All inquiries shall be sent in writing to FDABAA@fda.hhs.gov and will be forwarded to the appropriate technical contact.

CLASSIFIED SUBMISSIONS: Classified proposals will not be accepted.

USE OF COLOR IN PROPOSALS: All proposals received shall be stored as electronic images. Electronic color images require a significantly larger amount of storage space than black-and-white images. As a result, Offerors’ use of color in proposals should be minimal and used only when absolutely necessary for details. Do not use color if it is not necessary.

POST EMPLOYMENT CONFLICT OF INTEREST: There are certain post-employment restrictions on former federal officers and employees, including special government employees (Section 207 of Title 18, U.S.C.). If a prospective Offeror believes a conflict of interest may exist, the situation should be emailed to the Contracting Officer, prior to expending time and effort in preparing a proposal. The appropriate FDA personnel will discuss any conflict of interest with prospective Offeror’s.

UNSUCCESSFUL PROPOSAL DISPOSITION: Unless noted in an Offeror's proposal to the contrary, unsuccessful Full Proposals will be disposed of in accordance with FDA regulations.

Part IV: Proposal Evaluation

A. Evaluation Criteria:

The selection of one or more sources for award will be based on an evaluation of each Offeror’s Quad Chart and White Paper and Full Proposal. The Quad Chart and White Paper and Full Proposal will be evaluated by a peer or scientific review process based on the following criteria. The following criteria are in descending order of importance (Sub-criteria listed under a
particular criterion are of equal importance):

1. **Scientific and Technical Merit:**
The Government will evaluate the Overall scientific and technical merit of the proposal with respect to the following subfactors:

   - The degree of innovation and potential to offer a revolutionary increase in capability or a significant reduction in cost commensurate with the potential risks of the innovative approach.
   - The soundness, feasibility, and validity of the proposed plans, methods, techniques, and procedures of the technical proposal, to include the reasonableness of the proposed schedule and demonstrated understanding of the statutory and regulatory requirements for FDA licensure.
   - The Offeror's understanding of the scope and the technical effort needed to address it.

2. **Program Relevance**
The Government will evaluate how relevant the proposal is to the stated Agency Programs based on the how the proposal addresses the following questions/subfactors:

   - Does the project address an important problem or a critical barrier to progress in the field?
   - 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?
   - Do the training, professional development and research proposals address important needs and areas of regulatory science and will they inform future medical product development and regulatory decision-making?
   - If the project aims are achieved, how will technological advances, regulatory practice, and/or health be improved?
   - Will the new approach/methodology have a competitive advantage over existing/alternate approaches?
   - Does the proposed research address an unmet area in regulatory science?

3. **Capabilities and Experience:**
   - Overall capabilities, including the qualifications, capabilities, and experience of the proposed principal investigator, team leader, and key personnel who are critical in achieving the proposal objective; the Offeror's qualifications, capabilities, and experience in related technical areas; and the Offeror's facilities and demonstrated ability for achieving the proposal objectives. For proposals involving prototype development this will include availability (either in-house, through subcontract, or through industrial affiliates) of design and development tools/capabilities appropriate to the proposed prototype. Additionally, Offerors are strongly encouraged to develop partnerships with public and private entities in order to maximize the capabilities of the research team.

   - Research Management: Overall capability to manage the effort, including plans to objectively measure the value and impact of the research and ensure value whether the inquiry leads or does not lead to anticipated results.

**B. Past Performance Information**
Past performance information will be evaluated to the extent of determining the Offeror’s risk of successful contract performance.

The Government is not required to contact all references provided by the Offeror. The Government may use performance information obtained from other sources than those identified by the Offeror/subcontractor and may utilize existing databases of Contractor performance information (CPARS and PPIRS). Also, references other than those identified by the Offeror may be contacted by the Government to obtain additional information that will be used in the evaluation of the Offeror's past performance.

If the performance information contains negative information on which the Offeror has not previously been given an opportunity to comment, FDA will provide the Offeror an opportunity to comment on it prior to its consideration in the evaluation, and any Offeror comment will be considered with the negative performance information.

C. Cost Evaluation

Total Cost and Cost Realism

Each price/cost response will be reviewed for price/cost realism, reasonableness, and overall best value to the Government. Members of the review team may presume that the technical approach provided by the Offeror serves as a rationale for the labor mix and labor hours used.

Applicants must adequately address the following requirements:

- a. Research involving Human Subjects/Anatomical Substances (if proposed).
- b. Research involving Animals (if proposed).
- c. Evidence of GLP Compliance (if appropriate).
- d. Evidence of GMP Compliance (if appropriate).
- e. Evidence of GCP Compliance (if appropriate).
- f. Evidence of Laboratory Licensure Requirements (if appropriate)
- g. Use of Select Agents (if appropriate)
- h. All required Representations and Certifications are completed and on file.

Throughout the evaluation of Full Proposals Offerors may be asked to submit, to the Contracting Officer or Specialist, additional information and/or supporting documentation on the breakdown of costs in a full proposal. This information will be used to conduct a cost or price analysis necessary to justify that all costs in a proposal are fair and reasonable. Offerors must comply with requests for cost and pricing information to be considered for award.

Award Decision

The final evaluation will be based on an assessment of the overall best value to the government as it relates to the criteria above. Awards, if any, will be made considering the proposal evaluation, funds availability, and other programmatic considerations.
Part V: Attachments

Attachment 1: Summary of Related Activities

The following specific information must be provided by the Offeror pertaining to the Project Director, Principal Investigator, and each of any other proposed key professional individuals designated for performance under any resulting contract.

a. Identify the total amount of all presently active federal contracts/cooperative agreements/grants and commercial agreements citing the committed levels of effort for those projects for each of the key individuals* in this proposal.

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*If an individual has no obligation(s), so state.

b. Provide the total number of outstanding proposals, exclusive of the instant proposal, having been submitted by your organization, not presently accepted but in an anticipatory stage, which will commit levels of effort by the proposed professional individuals*.

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*If no commitment of effort is intended, so state.

c. Provide a statement of the level of effort to be dedicated to any resultant contract awarded to your organization for those individuals designated and cited in this proposal.

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Attachment 2: Government Notice for Handling Proposals

NOTE: This Notice is for the Technical Evaluation Review Panel who will be reviewing the proposals submitted in response to this BAA. THE OFFEROR SHALL PLACE A COPY OF THIS NOTICE BEHIND THE TITLE PAGE OF THE TECHNICAL PROPOSAL.

This proposal shall be used and disclosed for evaluation purposes only, and a copy of this Government notice shall be applied to any reproduction or abstract thereof. Any authorized restrictive notices which the submitter places on this proposal shall be strictly complied with. Disclosure of this proposal outside the Government for evaluation purposes shall be made only to the extent authorized by, and in accordance with, the procedures in HHSAR 352.215-1.

(f) If authorized in agency implementing regulations, agencies may release proposals outside the Government for evaluation, consistent with the following:

(1) Decisions to release proposals outside the Government for evaluation purposes shall be made by the agency head or designee;

(2) Written agreement must be obtained from the evaluator that the information (data) contained in the proposal will be used only for evaluation purposes and will not be further disclosed;

(3) Any authorized restrictive legends placed on the proposal by the prospective Contractor or subcontractor or by the Government shall be applied to any reproduction or abstracted information made by the evaluator;

(4) Upon completing the evaluation, all copies of the proposal, as well as any abstracts thereof, shall be returned to the Government office which initially furnished them for evaluation; and

(5) All determinations to release the proposal outside the Government take into consideration requirements for avoiding organizational conflicts of interest and the competitive relationship, if any, between the prospective Contractor or subcontractor and the prospective outside evaluator.

(g) The submitter of any proposal shall be provided notice adequate to afford an opportunity to take appropriate action before release of any information (data) contained therein pursuant to a request under the Freedom of Information Act (5 U.S.C. 552); and, time permitting, the submitter should be consulted to obtain assistance in determining the eligibility of the information (data) in question as an exemption under the Act. (See also Subpart 24.2, Freedom of Information Act.)
Attachment 3: Quad Chart and White Paper Format Template

I. Quad Chart Template

Any quad chart submitted that exceeds the one-page limit will not be evaluated. Please note that the Title of the Project should be different than that of the Topic.

TITLE OF PROJECT, MOST APPLICABLE RESEARCH AREA ADDRESSED
PROGRAM DIRECTOR/MANAGER, COMPANY NAME

| Objective: Clear, concise (2-3 sentences) description of the objectives and methodologies of the effort. | Picture or Graphic that illustrates the research or concept (e.g. data figures, molecule illustrations of processes) |
| Description of Effort: A bullet list (2-3) of the primary scientific challenges being addressed | |
| Benefits of Proposed Technology: | Bullet list of the major goals/milestones by Project Year |
| Challenges: | Proposed Funding: Base period cost plus each option period (no more than 5 years total) |
| Research and Development Justification: | Contact Information (name, email, phone) |

White Paper Technical Information:

1. In general, the White Paper should provide a brief technical discussion of the Offeror’s objective, approach, level of effort, and the nature and extent of the anticipated results. Specifically, the White Paper should include, at a minimum, the following core elements:
   a. brief discussion on how the proposed project aligns with the objectives of FDA Regulatory Science
   b. a clear, concise development plan for licensure that includes all non-clinical, clinical, manufacturing, and regulatory activities (i.e. as applied to the FDA’s animal rule) required for the proposed countermeasure.
   c. a high-level Gantt chart showing an overview of the proposed activities and timelines.
   d. a brief description of the Offeror’s intellectual property ownership of the proposed countermeasure.
   e. overview of Offeror’s capabilities and experience (past and current) as they relate to the proposed program.

2. The cost portion of the White Paper shall contain a brief cost estimate revealing all the component parts of the proposal.
3. As an addendum to the White Paper, include biographical sketches (two pages) of the key personnel who will perform the research, highlighting their qualifications and experience.

4. Offerors shall include a brief justification describing how the project falls under the FAR requirements for R&D work.

Restrictive markings on White Papers: Proposal submissions will be protected from unauthorized disclosure in accordance with FAR Subpart 15.207, applicable law and HHS regulations. Offerors that include in their proposal data that they do not want disclosed shall mark their proposal in accordance with the instructions contained FAR 52.215-1(e) “Restrictions on disclosure and use of data”. Please note that any white paper submitted under this solicitation may be shared with other government agencies for non-FDA funding considerations.
Attachment 4: Research and Development Justification

Broad Agency Announcements, as described in the Federal Acquisition Regulations (FAR), may only be issued for the procurement of Research and Development (R&D). The following are FAR definitions for Basic and Applied research and Development. All acquisitions resulting from this announcement must meet one or more of the FAR definitions below. All offerors shall write a justification describing why and how the proposal being submitted falls under one or more of the definitions for basic research, applied research and development. The justification shall be no longer than one (1) page in length, single spaced, using 12 point font.

- **Basic research** - Research directed toward increasing knowledge in science. The primary aim of basic research is a fuller knowledge or understanding of the subject under study, rather than any practical application of that knowledge (FAR 2.101(b)(2))
- **Applied research** - The effort that (a) normally follows basic research, but may not be severable from the related basic research; (b) attempts to determine and exploit the potential of scientific discoveries or improvements in technology, materials, processes, methods, devices, or techniques; and (c) attempts to advance the state of the art. When being used by contractors in cost principle applications, this term does not include efforts whose principal aim is the design, development, or testing of specific items or services to be considered for sale; these efforts are within the definition of “development,” given below (FAR 35.001).
- **Development** - The systematic use of scientific and technical knowledge in the design, development, testing, or evaluation of a potential new product or service (or of an improvement in an existing product or service) to meet specific performance requirements or objectives. It includes the functions of design engineering, prototyping, and engineering testing; it excludes subcontracted technical effort that is for the sole purpose of developing an additional source for an existing product and the development of a specific system or hardware procurement (See FAR 35.001).