FDABAA-21-00123

Overview Information

Agency Name: Department of Health and Human Services (HHS), Food and Drug Administration (FDA), 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, 4041 Powder Mill Rd. Beltsville, MD 20705

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

Announcement Type: Broad Agency Announcement (BAA)

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 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 5:00 pm, Eastern Standard Time, January 28, 2021, and earlier if possible. White papers submitted after that date will still be accepted, but due to a lack of lead time, will not be considered for award in FY21.

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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 on 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, ranging from pre-market review of efficacy and safety of many of its regulated products to post-market product surveillance, review of product quality, regulation of product manufacture, and 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. In order 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 below and further described in Part I of this announcement.

Research Areas of Interest:

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 www.beta.sam.gov using Keyword Search “FDABAA-21-00123.”

This BAA is a continuously open announcement valid throughout the period from the date of issuance through the closing date specified in the www.beta.sam.gov announcement. Amendments to this BAA, **if necessary**, will be posted in the same site when they occur. Interested parties are encouraged to periodically check the website for updates and amendments.

Part I: Research Areas of Interest

Through this BAA, FDA seeks to support advanced research and development strategies with potential for regulatory application in the following research areas of interest. This section presents the technical objectives that FDA seeks to achieve through this BAA. Because resources are limited, preference will be given to projects geared towards developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products. 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 (e.g. primary lung cells grown at an air liquid interface);

1.1.2. Develop new animal models that better mimic diseases to better understand the potential influence of disease progression and risk factors, including 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. 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

1.1.6. Develop methods for biocompatibility and toxicological risk assessments for new device materials In line with 21st Century Cures Least Burdensome measures and the reduction in the use of animals.

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

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

1.1.9. Develop computational tools and models to predict immunogenicity for biologic products including modified sequences for mitigation of immunogenicity risk.

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 better predict potential human and animal risk, both overall and/or in subpopulations;

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;

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

1.3. Develop and Use computational methods and in silico modeling:

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

1.3.2. Develop computer models of cells, organs, and systems (including the impact of hormones) to predict product risk, safety and efficacy;

1.3.3. Develop computational models to evaluate regulated-product toxicity or the safety and efficacy during pregnancy;

1.3.4. 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;

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

1.3.6. 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.

1.3.7. Develop rare-disease clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes, with attention to the challenges of small population and heterogeneity of patients with rare conditions.

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;

- 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;
- 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 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. 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.

2.1.8. Improve clinical study design and conduct to better identify and evaluate possible sex and gender differences related to FDA-regulated products

2.1.9. Improve clinical study design and conduct to examine diseases and conditions primarily affecting women across the lifespan (e.g., pregnant, lactating, pre- and post-menopausal and older women);

2.1.10. Explore the natural history and impact of COVID-19 on women’s health across the lifespan (e.g., pregnant, lactating, pre- and post-menopausal and older women).

2.1.11. Evaluate strategies for the prevention, diagnosis, and treatment of COVID-19 for

potential sex- and gender-based health effects.

2.2. Leverage existing and future data:

2.2.1. Develop quantitative models and measures of disease progression;

2.2.2. Develop natural history studies on both prevalent and rare diseases to identify disease subsets/phenotypes amenable to differential approaches for therapy or management, and possibly with novel biomarkers for their identification.

2.2.3. 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, gender, 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.

2.2.4. 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, wearables or digital heath technologies) to support regulatory decision-making.

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

2.2.6. 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 tools 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
- Using a collaborative approach, identify high-priority areas for development of real-world data source methodology that meet stakeholder needs
- Explore methodological reasons for discordant findings among randomized and observational analyses addressing the same clinical topic involving FDA-regulated products
- Advance causal interference using health care real world data

2.2.7. Develop core data elements and data sets for device categories to support regulatory decision making

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

2.2.9. Design and optimize data infrastructure to facilitate information exchange and data extraction.

2.2.10. Identify, develop, and evaluate data sources and efficient techniques for data mining, data linkage, and large data set analysis that can be used to assess the safety and effectiveness of FDA-regulated products, to specifically identify women's health issues.

2.2.11. Develop and validate a tool that uses natural language processing, machine learning and artificial intelligence to semi-automate review of medical charts to improve, expedite and lower chart review costs.

2.2.12. Develop and improve the efficiency of signal detection/data collection methods and

operations such as computable phenotype generation in support of future postmarket active surveillance systems for CBER-regulated biologics and drugs

2.2.13. Identify and develop interfaces to access new, large medical databases such as EHR, claims, registries and others to improve safety and effectiveness evaluations of patient subpopulations such as pediatric, elderly, rare diseases, both sexes, different genders and others.

2.2.14. Identify and develop access infrastructure to new regulatory quality EHR data sources that use SMART on FHIR, ISBT-128 coding for use in studying safety or effectiveness of blood, blood products, cellular products and others.

2.2.15. Develop methods and conduct studies that replicate findings of randomized controlled trials of CBER-regulated biologic products using regulatory quality real-world data for specific studies of biologic products.

2.2.16. Compare use of RWD and generation of RWE with more traditional approach methods for data collection and evidence generation.

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. Develop and evaluate novel approaches for biomarker identification, including -omics, systems biology, and high throughput methods. Other approaches may include pharmacodynamic response - dose selection, disease severity, progression and prognosis, and pharmacogenomics (to predict safety and efficacy or guide dosing).

2.3.2. Identify and evaluate biomarkers to be used in the assessment of products related to conditions that affect women and identify sex differences in biomarkers related to the performance of medical products

2.4. Facilitate Antimicrobial Drug Development and Address Antimicrobial Drug Resistance

Antimicrobial drug resistance is a major threat to public health. FDA's roles in combatting Antimicrobial drug resistance is to: (1) facilitate the development of new antibacterial, antifungal 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 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, pharmacokinetic studies, and/or real-world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction (for more background, see link: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-infectious-diseases-research-activities

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

2.4.4. Advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship. For example, provide updated data from microbiologic surveillance studies, pharmacokinetic studies, including modeling, and/or clinical outcome data to support updating susceptibility test interpretive criteria for certain antibacterial drugs that are a high public health priority. (for more background, see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-infectious-diseases-research-activities)

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

Serious Mental Illness (SMI) is a major concern 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 of 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. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Outcomes in Diverse Populations

2.6.1. Identify methods to improve data collection in clinical trials for racial and ethnic minorities, as well as rural and underserved populations (rural, elderly).

2.6.2. Identify develop and evaluate data sources and efficient techniques for data mining, data linkage, and large data set analysis that can be used to assess the safety and effectiveness of FDA-regulated products among racial and ethnic minorities and underserved populations.

2.6.3. Assess the prevalence of biomarkers among racial and ethnic minorities used in the design and enrollment of clinical trials and their implication for drug and device development.

2.7. Immuno-oncology

OCE is particularly interested in supporting research to improve understanding of atypical response patterns observed in patients treated with immune checkpoint inhibitors (ICIs), to develop endpoints that further development of cancer immunotherapy and cancer immunotherapy combination regimens, and to identify and characterize patients with resistance to cancer immunotherapy (additional background information relating to these

areas of interests may be found here https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific-collaborative):

2.7.1. Perform analyses of clinical data to develop a better understanding of the proportion of patients with atypical response and explore the development of predictive analytics related to ICI treatment.

2.7.2. Develop technologies and approaches that better predict or characterize atypical response patterns to ICI such as radiomics, circulating tumor DNA, and/or novel approaches for immune cell profiling of the micro environment.

2.7.3. Develop clinical trial endpoints that account for atypical response patterns and more fully characterize the clinical benefit of ICI and other cancer immunotherapies.

2.7.4. Develop biomarkers and/or pharmacodynamic end points to demonstrate the effect of ICI in cancer immunotherapies or as part of a combination regimen.

2.7.5. Analyze RWD to understand the utilization and impact of complementary in vitro diagnostics in cancer immunotherapy.

2.7.6. Support research to improve understanding of the side effects of ICIs.

2.8. Cell /Gene and Personalized Neo-antigen-based Therapies for Cancer

OCE is interested in supporting research related to clinical development, safety, manufacturing and quality control for cell therapy and neo-antigen-based therapies for cancer, specifically to: (additional background information relating to these areas of interests may be found here https://www.fda.gov/about-fda/oncology-center- excellence/oce-scientific-collaborative)

2.8.1. Facilitate regulatory review of neoantigen-based cancer therapies by supporting research to:

- Develop, optimize and standardize algorithms for neoantigen identification. These are important to ensure the efficacy and safety of these products in the treatment of patients with cancer.
- Create novel technologies and approaches to evaluate both efficacy and safety for neoantigen-based therapies that incorporate unique features of individual cancers, neoantigen and immune responses. Examples may include neoantigen-based vaccines and redirecting the T-cell specificity by genetically modifying T cells with receptors specific against neoantigen-derived epitopes.

2.8.2. Implement innovative clinical trial designs for a group of cell or neoantigen-based therapies that were developed using a common platform (but target distinct antigens) to compare safety and clinical activity among products to identify the most promising candidates for further development.

2.9. Health Equity and special populations in oncology drug development

O CE is interested in understanding the factors that affect the safety and treatment response in demographic subgroups that have been historically underrepresented in oncology trials (e.g., racial/ethnic minorities, sexual and gender minorities, older adults), specifically to:

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific-collaborative.

2.9.1. Conduct qualitative research to understand barriers to including underrepresented groups in oncology clinical trials (e.g., ageism, bias, patient and/or physician preference)

2.9.2. Identify best practices for enrolling underrepresented subgroups in oncology clinical trials, including patient-, physician-, and community-focused approaches. Evaluate the

effectiveness of interventions designed to enroll diverse populations in oncology clinical trials such as digital technologies, decentralized clinical trials, patient/community/language navigators.

2.9.3. Improve data collection in oncology clinical trials relevant to underrepresented subgroups.

2.9.4. Characterize the prevalence of currently druggable biomarkers in racial/ethnic minorities and assess implications for enrollment in clinical trials.

2.9.5. Understand the impact of remote assessments and decentralized procedures (e.g., e-consent, telemedicine, collecting laboratory and/or imaging data from local facilities) on underrepresented subgroups participating in oncology clinical trials.

2.9.6. Conduct RWD studies to improve understanding of safety and efficacy of drugs in underrepresented groups such as analyses of low-grade toxicities, symptom function measures, and co-morbidities.

2.9.7. Study RWD to understand patterns of care and clinical outcomes in sexual and gender minorities with cancer.

2.10. Oncology trial designs, end points and statistical methodologies

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific-collaborative)

2.10.1. Develop novel statistical approaches for using external controls in oncology trials, which could supplement concurrent control arm data and address key challenges such as differences in eligibility criteria, exposure, and outcomes between external control and clinical trial patients; bias, and rapidly evolving standards of care.

2.10.2. Multi-disciplinary research that includes expert clinical and statistical input addressing how external control data can be used to isolate the treatment effect of experimental combination therapies.

2.10.3. Develop, define and test real world oncology endpoints from RWD that could be used to generate real world evidence (RWE) to complement traditional clinical trial data submitted to FDA.

2.10.4. Explore and define RWD quality to consider factors including data variable collection, specificity, sensitivity, data provenance, data linkage, data validation, harmonization, and the potential capability to make inferences from the available data.

2.11. Pediatric Oncology

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center- excellence/oce-scientific-collaborative)

2.11.1. Development of preclinical models (e.g., patient-derived xenograft models, orthotopic mouse models, organoids) of pediatric tumors, most of which are embryonal in origin to facilitate decision-making regarding the evaluation of emerging novel agents potentially applicable to tumors which predominantly occur in the pediatric population.

2.11.2. Investigations to elucidate the relevance of specific molecular targets to the growth and/or progression of pediatric tumors to understand and assess target actionability using text mining and artificial intelligence to analyze, assess and interpret the scientific literature and other public databases of genomic and transcriptomic analyses of pediatric cancers

2.11.3. Translational research to design and develop rational combination regimens for pediatric patients that may include immune checkpoint inhibitors (ICIs) and other treatments (e.g., chemotherapy, vaccines, radiation) based on a strong scientific

rationale that addresses the current data suggesting lack of activity of single agent ICIs in pediatric tumors

2.11.4. Investigations to explore opportunities to develop acceptable external control arms from using real world evidence to aid in accelerating new drug approvals for childhood cancer.

2.11.5. Development of immune based therapies (engineered immune effector cells or bifunctional activators) that recognize tumor specific altered glycan epitopes (glycolipids or glycoproteins) that NK and T-cells do not generally recognize.

2.12. Precision Oncology

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center- excellence/oce-scientific-collaborative.

2.12.1. Develop algorithms that predict an individual patient's genotype and/or response (in terms of efficacy and/or safety) to cancer therapy using different types of medical images including radiology images (e.g., CT, PET) and/or histopathology images combined with novel analysis approaches such radiomics and machine learning.

2.12.2. Identify biomarkers (including liquid biopsy biomarkers) to gain information related to oncology diagnosis, monitoring, response, or resistance.

2.12.3. Conduct studies to compare the performance of local and centralized molecular tests used for patient enrollment on cancer clinical trials.

2.12.4. Conduct studies to understand why tumors located at different organ sites with molecular alterations in the same target respond differently to therapies to inform future potential tumor agnostic drug development.

2.12.5. Develop methodologies to inform clinical trial design of liquid biopsy studies that are assessing multiple cancer types simultaneously for early detection indications.

2.12.6. Conduct retrospective or prospective studies/biomarker evaluations to understand if there are differences in response to targeted cancer treatment based on somatic vs. germline alterations of the target gene.

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, or
- Outcome can include, but is not limited to, trainings on the methods.

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 and characterization for

equivalence or similarity comparison. Some specific areas of research could include: (1) appropriate analytical methods, including bioassays, 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.

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), biological products (e.g., therapeutic proteins or monoclonal antibodies) and complex dosage forms (e.g., transdermal patches, inhalation delivery systems, and targeted drug delivery systems) in FDA-regulated products.

3.1.4. Develop and evaluate practical in-process monitoring systems, methods, and metrics for advanced manufacturing processes including additive manufacturing, process intensification until operations, or adaptive and automation operations.

3.1.5. Develop and evaluate the use of model-based digitally integrated systems, artificial intelligence, machine learning and simulation in production or quality system activities. Proposals may include but are not limited to:

- Generative Design
- Production simulation and simulated process validation
- AI/ML application to quality system activities, such as, complaint management, trending, or others
- Intelligent Design Control
- Closed loop risk-management

3.1.6. Explore novel applications of advanced (e.g. integrated and 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 these technologies. Additionally, proposals should clearly quantify the improvement metric for implementation of advanced manufacturing processes 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
- Novel in-line and real time monitoring technologies
- Improved cell lines for continuous viral vector production and improved vector purification technologies
- Advanced manufacturing technologies for cell cultures used to manufacture vaccines

3.1.7. Refine or enhance existing technologies to improve the sensitivity, specificity, and robustness of testing methods used to measure medical countermeasure (MCM) potency, in-process characteristics, and final drug substance characteristics (for example, in-line sensors and process analytical technologies)

3.1.8. Advance broadly-applicable, commercially-ready (manufacturing readiness level {MRL} 4-61) tools, technologies, and platforms that improve manufacturing efficiency, consistency, quality, and speed of medical countermeasures (MCMs) to bolster the MCM supply chain; for example, “plug-and-play” modular unit operations applicable for downstream processing, or continuous manufacturing.

3.1.9. Investigate the effects in supply chain of implementing advanced manufacturing for specific types of medical products, especially such as biologics, vaccines and medical devices. Topics may include:

- Supply chain resilience to disruption
- Increased access
- Personalization
- Decreased reliance on foreign supply chains.

3.2. Develop new analytical and in vitro release 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.

3.2.4. Develop patient-focused quality standards or specifications by establishing, evaluating and validating in vitro release methods (e.g., dissolution methods) that predict in vivo performance for various dosage forms (e.g., solid oral dosage forms).

3.2.5. Genetically modified animals: Investigate new analytical methods to identify unintended genomic modifications introduced using genome editing or other modern molecular biology techniques and to differentiate these changes from naturally occurring mutations.

3.2.6. Genetically modified animals: Develop new analytical methods to screen for the occurrence of unintentional genomic modifications during commercial production in which intentional genomic alterations are introduced.

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 management maturity, including quality metrics and quality culture, supply chain oversight, inventory management, application of risk management, manufacturing operations, quality management systems, and continuous improvement in domestic and foreign establishments. Adaptable and reproducible approaches are needed to inform consistent assessment of robustness of a manufacturer’s quality management maturity. Develop methods for data collection, validation, and assessment of appropriate and robust metrics.

3.3.2. Advance statistical methodology, including data mining and machine learning, for assessing disparate data types and sources in the evaluation of products, manufacturing facilities and quality systems and processes to support post-market

[1] Manufacturing Readiness Levels as defined by Department of Defense: http://www.dodmrl.com/ and further explained at: https://www.nextflex.us/wp-content/uploads/NextFlex_PC3.0_MRL-TRL_Definitions.pdf

quality surveillance programs.

3.3.3. Develop and evaluate methods for prioritizing quality defect report assessment, surveillance sampling, and surveillance inspection scheduling.

3.3.4. Develop and evaluate methods for estimating the state of quality for products and facilities that enable cross-sectional comparisons and quantitative ratings.

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.

3.4.4. Develop sensitive, rapid methods to detect, identify, and enumerate communicable disease contaminants (i.e., viral, prion protein) and validate their utility in assessing product contamination

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 2020 topic areas are as follows:

3.5.1. Post-market Evaluation of Generic Drugs

- Develop surveillance and monitoring methods for generic drug substitutions.
- Understand patient perceptions of generic drug quality and effectiveness.

3.5.2. Complex active ingredients, formulations, or dosage forms

- Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients
- Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products
- Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products
- Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables including the identification of the critical quality attributes (CQA) and drug release mechanisms for these products
- Advance characterization tools for polymeric excipients and related complex formulations to provide product specific guidance on qualitative sameness assessment and explore alternative bioequivalence approaches

3.5.3. Complex routes of delivery

- Improve Physiologically-Based Pharmacokinetic (PBPK) models of drug

absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic) to allow their use in supporting alternative BE approaches

- Enhance understanding of excipients on topical drug absorption to evaluate invitro BE methods for non-Q1/Q2 topical drug products applied to skin or other local areas
- Implement in vitro methods together with PK and certain other methods as alternative to the use of comparative clinical endpoint BE studies for nasal and inhaled drug products

3.5.4. Complex drug-device combinations

- Evaluate the impact of identified differences in the user-interface from the RLD on the therapeutic equivalence of complex generic drug-device combination products
- Develop criteria for device performance comparisons that would support a BE demonstration by in vitro methods and eliminate the need for in vivo BE.

3.5.5. Tools and methodologies for bioequivalence and substitutability evaluation

- Improve quantitative pharmacology and BE trial simulation to optimize design of BE studies for complex generic drug products and establish a foundation for model-based BE study designs.
- Integrate predictive dissolution, PBPK and Pharmacokinetic/Pharmacodynamic (PK/PD) models machine learning to evaluate in vitro BE options for orally administered drug products and support global harmonization of the most the most efficient BE recommendations
- Develop alternative BE approaches to account for unexpected events such as COVID-19-related study interruptions and protocol deviations
- Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System (BCS) of Class 3 biowaivers to drug products with differences in formulations larger than currently recommended in FDA guidance
- Develop methods and integrated technological solutions that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution/utilization patterns, drug safety data, and drug quality data) to support regulatory decisions and improve post-market surveillance of generic drug substitution

3.6. Identify and Qualify Biomarkers that are Associated with Therapeutic Response in Animals

3.6.1. Identify and validate endpoints, including clinical pain assessment tools and/or molecular biomarkers (proteomic or genomic), that can be used to evaluate the effectiveness of therapeutic agents to alleviate pain in food animals such as cattle, pigs, and goats.

3.6.2. Identify molecular biomarkers (proteomic or genomic) that can be qualified to serve as clinical surrogate endpoints in assessing the capacity of therapeutic agents to modify the pathophysiology of diseases in dogs, cats, horses, or other companion animals.

3.7. Develop a Regulatory Database for Species Identification

3.7.1. Develop a DNA barcode sequence database for species identification, including for

botanical products

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.

- 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.
- 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.
- 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.
- 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.
- Develop methods for efficiently communicating design vulnerabilities such as tools for analyzing cybersecurity risk (e.g. threat modeling, attack trees) to increase stakeholder understanding of cybersecurity considerations and risks.

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 gene and cell therapies

4.1.1.2. Development of reference materials and standards for gene and cell therapies

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

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 technologies in the evaluation of 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 and combination product design and review.

4.1.7. Examine sex and gender differences early in the development of innovative health products, new materials, and novel assessment tools and methodologies, including nanotechnology, precision medicine, pharmacogenomics, novel imaging and diagnostic technologies, 3-D printing, stem cells and regenerative medicine, and In-silico modeling.

4.1.8. Explore the impact of COVID-19 and the use of novel therapies on women's health.

4.2. Evaluate technologies designed to reduce nonmedical use and overdose involving opioids and other medications with abuse potential. Areas of interest include:

4.2.1. Perform research to enhance FDA's understanding of the features of existing and emerging packaging, storage, delivery and disposal solutions that can reduce nonmedical use of opioids and other medications with abuse potential, and the evidence available to support these features. Features may include the retrievability of active ingredient, cost, ease of use, safety messages, or package size/quantity.

4.2.2. Identify and evaluate appropriate endpoints for studies undertaken to assess packaging, storage, delivery and disposal solutions designed to reduce nonmedical use of opioids and other medications with abuse potential. Endpoints may include accidental poisonings, use of disposal options to discard leftover medication, medication adherence, unauthorized access of medication, amount of leftover medication, unintended consequences, and others.

4.2.3. Compare direct measures of the extent of patient disposal of opioids and other medications with abuse potential across:

4.2.3.1. various prescription medication disposal options provided to patients, or

4.2.3.2. provision of provision of education alone versus provision of a prescription medication disposal option

4.2.4. Assess the uptake, benefits, and harms of making available fixed-quantity unit of use blister packages of opioid analgesics. Consider differences in uptake of packages with and without recommendations or cues (e.g., order sets, electronic prescribing software cues/positioning) to use the packages.

4.2.5. Conduct behavioral economic or human factor analyses to assess prescriber, pharmacist, and patient reasons for use, knowledge, attitudes, beliefs, and challenges in accessing and using packaging, storage, delivery, and disposal solutions for opioid analgesics. Consider factors such as cost, design features, availability, stigma, and perceptions of risk.

4.2.6. Perform research to enhance FDA's understanding of patient perspectives on abuse deterrent formulations of medications.

4.3. Evaluate drug safety in pediatric populations, which requires sources and methods for

accurately measuring exposure (i.e. drug utilization) and outcomes. Areas of interest 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 inpatient and outpatient pediatric populations

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

4.4 Develop and facilitate innovative technologies toward universal pathogen reduction of the blood supply.

4.4.1. Identify and evaluate innovative treatments and technologies that inactivate known and emerging blood-borne pathogens in ex vivo stored whole blood, while preserving the quality and functions of the individual blood components for transfusion.

4.4.2. Develop new and improved technologies to expand the range of whole blood pathogen inactivation (e.g., demonstrate inactivation of parvoviruses, bacterial spores or prions).

4.4.3. Develop novel reagents and methods that can mitigate adverse effects associated with pathogen inactivation treatments to improve the quality of blood components for transfusion compared to existing licensed methods.

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

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 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.

5.1.4. 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.

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 and evaluate data sources and efficient techniques for data mining, linkage, and large-scale analysis that can be used to assess real-world evidence, including postmarket safety and utilization of FDA-regulated products to specifically identify sex and gender differences or women's health issues.

5.2.10. Examine the impact of COVID-19 on women's health across the lifespan (e.g., pregnant, lactating, pre- and post-menopausal and older women).

5.3. Computer Modeling and Simulation to Assess Product Risk

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

5.3.2. 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. Correlate these patient experience data to product quality management maturity at the firm level.

5.4.3. 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).

5.4.4. Develop and validate patient-reported outcome measures (PRO).

5.4.5. Adapt or update existing fit-for-purpose Clinical Outcome Assessments (COAs) for new populations, indications, or situations (e.g. expanding from adult to pediatrics) Develop patient-centered assessment tools and methodologies to reduce the burden of participating in clinical trials for patients. For example, a clinical trial can use mobile apps to collect timely response directly from patients to inform regulatory decisions.

5.4.6. Develop and test methods to convey differences in sampling methods to those collecting the patient experience data described in the guidance document, Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Discuss pros and cons of different approaches and provide practical advice on how to carry out each method using multiple scenarios for demonstration.

5.5. Systems Modeling of the Opioid Crisis

FDA is seeking innovative research to help understand the dynamics of the opioid crisis and the potential impact of interventions to address it. FDA is currently developing a system dynamics model of opioid crisis, aligned with recommended of the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) report entitled Pain Management and the Opioid Epidemic. The purpose of the model is to support FDA's and others' in a) better understanding the complexity of the interconnected mechanisms of the crisis, and b) assessing the potential impacts (intended and unintended) of possible policy actions to address the crisis. FDA is seeking complementary approaches to augment and support FDA's modeling efforts by generating novel data, data synthesis or evidence-based quantitative estimates addressing various complex aspects of the crisis, which can be translated into FDA evolving systems model. Specific topic areas include (but are not limited to):

Healthcare provider decision making and behaviors regarding opioids prescribing and treatment management, and the factors that most influence these decisions. Such factors may include but are not limited to: perceptions, training, healthcare systems, formularies, cost, and prescribing requirements. Various data sources and research and analytical approaches may be appropriate.

Fentanyl, stimulants, and/or poly-substance use and their interactive effects on opioids use, misuse, overdose, addiction, use disorder, treatment, and associated outcomes. Related topic areas may include influences on polysubstance use and overdose harm reduction.

Social media as a source of data on various aspects of the opioids system that may inform model development.

Adapting learnings from systems analysis of the opioid crises to support modeling and decision making in other emerging crises, e.g., the COVID-19 epidemic. Developing system dynamics models for other high-impact evolving situations.

5.6. Longitudinal Data to Study Trajectory of Substance Use Disorders:

5.6.1. Demonstrate the feasibility (e.g., by collecting pilot data) of assembling and following a prospective cohort in an enriched population of individuals at elevated risk for development or progression of substance use disorders. The objective of this work is to facilitate longitudinal studies that address important knowledge gaps about the natural history of substance use behavior, substance use disorders, and treatment engagement and outcomes. Recruit individuals who report nonmedical use of pharmaceutical products, for example opioid analgesic, stimulant, or sedative medications. Collect detailed baseline and follow-up data such as recent drug use behaviors, social and demographic characteristics, treatment history, safety measures, and severity of substance use problems. Report recruitment and retention metrics, including differences in these metrics by demographic and clinical characteristics. Demonstrate or perform validation of instruments used to collect baseline and follow-up information.

5.7. Oncology Patient-Focused Drug Development

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about- fda/oncology-center-excellence/oce-scientific-collaborative)

5.7.1. Investigate measurement characteristics for new and existing patient-reported global items quantifying overall side effect impact such as the FACIT GP5 item for patients undergoing anti-cancer therapy.

5.7.2. Evaluate differences in clinical outcome measures of physical function in an advanced cancer patient cohort undergoing treatment by prospectively capturing data from (a) electronic PRO, (b) wearable technologies, (c) performance outcomes and (d) clinician assessment (e.g. ECOG/Karnofsky).

5.7.3. Conduct a prospective study to compare the sensitivity and measurement characteristics of patient-reported physical function items using a 7-day recall period versus no recall period using a well-defined PRO physical function scale such as the PROMIS physical function bank.

5.7.4. Implement PRO symptom and functional measures using ePRO in advanced cancer patients using the FDA MyStudies application to test feasibility, accuracy and ease of use.

5.7.5. Investigate the sensitivity and measurement characteristics of existing patient-reported physical function measures in patients with rare and ultra-rare cancers.

5.7.6. Develop longitudinal analysis and visualization methods to communicate physical function trajectory over time in patients with advanced/metastatic malignancies.

5.7.7. Investigate individual-level change (i.e., responder definition) and meaningful change thresholds for PRO symptom measures using qualitative research methods to inform future quantitative studies in advanced cancer patients.

5.8. Oncology Safety

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center-excellence/oce- scientific-collaborative)

5.8.1. Develop approaches for collecting safety data from RWD sources to expand understanding of the safety profile of approved oncology drugs in clinical practice.

5.8.2. Develop approaches using RWD sources to evaluate the toxicity profile of approved drugs in cancer patients with a history of or active COVID-19 infection including any increase in known drug adverse reactions or new toxicities, longitudinal sequelae, and outcomes.

5.8.3. Develop improved and standardized approaches to collect and analyze cardiotoxicity data in the context of clinical trials and clinical practice.

5.8.4. Analyze RWD to help understand which patients are most likely to experience cardiotoxicity (or other types of severe toxicity) during cancer treatment.

5.8.5. Conduct basic, translational or clinical studies that investigate the underlying causes of cardiac toxicities associated with approved oncology agents.

5.8.6. Conduct translational studies that investigate underlying causes of recent safety alerts issued by FDA oncology.

5.9. Rare Cancers

(additional background information relating to these areas of interests may be found at https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific- collaborative)

OCE is interested in supporting research to assist drug development for rare cancers, defined by the Orphan Drug Act as a disease or condition that affects fewer than 200,000 people in the U.S. and includes several molecularly-defined subsets (e.g., RET-positive lung cancers) and all pediatric cancers such as:

5.9.1. Studies to investigate the natural history of rare cancers to provide clinical and scientific context to inform the design and interpretation of clinical trials.

5.9.2. Studies to develop and characterize symptom function measures for rare cancers to complement information obtained from traditional clinical trial endpoints used in regulatory submissions.

5.9.3. Innovative approaches to identify new biologically-driven opportunities for clinical development of previously approved drugs (or drugs for which development has been discontinued) in rare cancers.

5.9.4. 5.8.4 Studies in rare cancers to implement a clinical trial protocol incorporating use of telemedicine and/or decentralized approaches (e.g., collecting laboratory and/or imaging data from local facilities) for patient assessments to facilitate enrollment of patients with rare cancers.

5.10. Other Rare Diseases

5.9.1 Explore mechanisms to support and expedite development of approved drugs for other (non-cancer) rare disease indications (i.e., repurposing) such as analyzing real world data (e.g. registries) to inform screening and evaluation of drugs in rare populations.

5.9.2 Pilot a study in up to five rare (non-cancer) diseases to implement a clinical trial protocol incorporating use of telemedicine approaches for patient assessments. Proposed studies should focus on evaluating feasibility and implementation, including an analysis of the risks and benefits of different technologies, impact on clinical trial participation and the quality of data collected.

5.11. Oncology Real World Data (RWD) Utilization

Developing approaches to evaluate, integrate, and facilitate the use of oncology real world

data (RWD) e.g., electronic health records, administrative health claims, drug or disease registries, patient reported or generated health data to generate high quality real world evidence (RWE) is an active area of regulatory science as noted in the 21st Century Cures Act. Methodologically rigorous studies which expand upon the need to evaluate study designs, data quality, statistical approaches, and real-world endpoints specifically through scientific research studies, metric or framework development, or standardized definitions, are encouraged. Specific examples of interest are included in the immuno-oncology, health equity and special populations in oncology drug development, oncology trial designs, endpoints and statistical methodologies, pediatric oncology, oncology safety, and rare cancers sections of this document.

5.12. Harness Diverse Data to Improve Health Outcomes in Diverse Populations

5.12.1. Develop and analyze large scale clinical data sets to determine comparability of non-US data to the US population.

5.12.2. Refine methods for analysis of large healthcare databases and electronic health records to advance understanding of treatment outcomes by race/ethnicity and geographical location.

5.12.3. Conduct studies among racial and ethnic minorities and underserved groups (rural, elderly) that investigate patient preferences in benefit-risk assessments to advance understanding and aid regulatory decisions.

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 Foods Program to enhance detection and removal of unsafe contaminants from the Nation's food and feed supply. 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. 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

F DA 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 is to develop the tools, standards, and approaches to assess the safety, quality, and performance of MCMs and to help translate cutting-edge science and technology into innovative, safe, and effective MCMs. Additional information on the FDA MCMi initiative and projects is available at:

https://www.fda.gov/emergency-preparedness-and-response/medical-countermeasures- initiative-mcmi/mcm-regulatory-science

FDA reviews proposals for the potential of Dual Use Research of Concern as defined and in accordance with USG policy:

https://www.phe.gov/s3/dualuse/Pages/default.aspx

Offerors to Area 7 are encouraged to coordinate with FDA OCS, Office of Counterterrorism and Emerging Threats, via the OAGS point of contact for any questions or concept discussion prior to submission. In FY2021, FDA is encouraging the submission of SARS-CoV-2/COVID-19 and modernization of influenza vaccines related topics under Area 7 (per Executive Order 13387).

Areas of interest include:

7.1. Develop, characterize, and qualify tools to support MCM development under the Animal Rule or Accelerated Approval[2]

7.1.1. Advance the capability to conduct natural history studies necessary to support MCM development under the Animal Rule (e.g., further the understanding of the pathophysiological mechanisms of toxicity, species specificity, or virulence of challenge agents)

7.1.2. Develop improved in-silico models to extrapolate pharmacokinetic/pharmacodynamic (PK/PD) data from animals to humans (e.g., PK modeling, PK/PD modeling, physiologically-based pharmacokinetic (PBPK) modeling, or population modeling)

7.1.3. Develop and validate methods to better characterize the PK profile of MCMs (e.g., assays for measuring MCM concentration in appropriate body fluids)

7.1.4. Develop methods to assess interspecies differences in absorption, distribution, metabolism, and excretion (ADME) of MCMs to support effective dose selection

7.1.5. Identify and qualify biomarkers and immune correlates of protection that enhance the understanding of the mechanism of action of MCMs, support appropriate clinical dosing of MCMs, and enable comparisons to be made between animal model species and humans.

7.1.6. Develop and qualify in vitro systems (e.g., microphysiological systems) that can accurately predict in vivo responses in humans to complement the use of in vivo animal models to assess safety and efficacy of MCMs.

7.1.7. Develop, qualify, and/or facilitate innovative analytical technology or quantitative

[2] 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

imaging modality assessments of tissues/cells infected with emergent diseases and biological threats in order to advance characterization and further scientific understanding of pathophysiological mechanisms of infection, disease progression, susceptibility, or virulence.

7.1.8. Identify and evaluate biomarkers and predictors of harm, susceptibility, latency, or virulence of emergent diseases and biological threats using innovative analytical technologies, imaging modalities, and other advanced approaches (e.g. omics).

7.1.9. Develop or characterize new in vitro, ex vivo, or in vivo alternative models of infectious diseases or biological agent exposure that better mimic clinical events or specific patient populations in order to better understand the influence of exposure or disease progression on risk factors, including disease co-morbidities on the emergence of adverse events.

7.1.10. Develop and/or advance the capability to conduct in vitro or in vivo assessments with emergent infectious diseases or biological threats, at greater than or equal to Biosafety level 3 containment, in order to:

7.1.10.1. further scientific understanding of the pathogenesis of disease or exposure and the pathophysiological mechanisms of disease, toxicology, progression, susceptibility, or virulence;

7.1.10.2. investigate pathogenesis and pathophysiological mechanisms in alternative models of special populations, such as juveniles and patients with underlying medical conditions or rare diseases;

7.1.10.3. identify potential biomarkers of harm, toxicological effects, susceptibility/resistance, latency, or virulence.

7.2. Modernize tools to evaluate MCM product safety, efficacy, and quality; and secure the MCM supply chain:

7.2.1. Enhance capabilities to rapidly assess the safety, efficacy and/or effectiveness of MCMs used during public health emergencies including:

7.2.1.1. develop and refine tools and methodologies to collect, monitor, track, and analyze real-world data and real-world evidence to support regulatory decision making.

7.2.1.2. develop capabilities to inform or support clinical studies including pre-positioned protocols, rapid and flexible clinical trial designs, novel statistical methods for analysis of clinical data, and clinical trial networks.

Information on FDA MCM monitoring, and assessment projects is available at:

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

7.2.2. Develop and validate reference materials to facilitate the development of vaccines, therapeutics, and diagnostics related to relevant CBRN threat agents and emerging infectious diseases

7.2.3. Develop new tools and methodologies to leverage large, unstructured data sets for analysis of MCM-relevant safety and efficacy endpoints

7.2.4. Develop technologies that can rapidly detect counterfeit, substandard, or adulterated MCMs

7.2.5. Develop technologies that can support the rapid assessment of MCMs for shelf-life extension

7.2.6. Develop technologies and methods to monitor and predict disruptions in medical device/medical product supply chain. security due to technological or CBRN threats (see BAA Area 3.1.2)

7.3. Advance the development of tools to enable the rapid development and availability of investigational MCMs

7.3.1. Develop and validate rapid testing methods to speed characterization, in-process testing, and/or lot release for MCMs (e.g. sterility, immunogenicity, neurovirulence, mycoplasma, etc.)

7.3.2. Develop technologies to support the adoption of advanced manufacturing technologies for MCMs (see BAA Area 3.1.7 and 3.1.8)

7.3.3. Evaluate methods for facilitating and incentivizing the production and development of MCMs or MCM supply chain within the U.S (see BAA Area 3.1.9).

7.3.4. Develop and/or advance the capability to conduct in vitro or in vivo assessments with emergent infectious diseases or biological threats, at greater than or equal to Biosafety level 3 containment, in order to:

7.3.4.1. identify measurable characteristics of toxicological effects, safety and efficacy when evaluating therapeutic regimens and/or interventions to enable translational comparisons between animal model species and humans and to support clinical dosing; or

7.3.4.2. identify interactions between therapeutics, characteristics of alternative models of special populations, and disease variables influencing efficacy and adverse event outcomes.

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

FDA seeks to identify and improve science-based approaches, (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. The following six priority areas are those in which FDA seeks to enhance its communications.

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 and authorized 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 consumers, patients, health care providers, health educators and informal caregivers.

8.1.2. Identify elements of OTC drug labeling that are confusing to consumers, particularly persons with low literacy and low numeracy. Study ways to improve labeling to better communicate information necessary for safe and effective use.

8.2. Explore ways that FDA communications can best complement those communicated by industry and other organizations 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 other communication materials (e.g. webpages, social media), by FDA communications, and by messages developed by other organizations among patients and consumers, including those with low literacy and limited English proficiency

8.3. Assess public understanding of regulatory terms

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 but are not limited to the following: "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 and/or labeling/packaging 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.

8.5.1.5. Develop methods and carry out studies to better understand the trajectory of stimulant use disorder. Factors to consider include the role of illicit vs. prescription stimulants, patterns of single substance use vs. polysubstance use, and treatment goals and behavior of individuals with stimulant use disorder.

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 pilot new technologies that can be used to integrated REMS requirements into the healthcare system.

8.6.1.2. Evaluate patients' and healthcare providers' preference on how risk information is conveyed and develop new and improved methods to communicate risk information to patients and healthcare providers.

8.6.1.3. Identify and evaluate best practices for healthcare provider and patient engagement in REMS design and modification

8.6.1.4. Identify and develop informative REMS assessment metrics, outputs and outcomes (including performance thresholds) indicating at which point REMS goals and objectives have been achieved.

8.6.1.5. Develop and refine data analysis methods (e.g. control charts) to better understand provider and patient adherence to REMS requirements leveraging data from external sources such as insurance claims and electronic health records.

8.6.1.6. Use social and behavioral science methods in conjunction with large electronic healthcare data to enhance the understanding of factors (e.g. system -, provider-, and patients-level characteristics) that affect REMS program design, implementation, and effectiveness.

8.6.1.7. Identify RWD or other data sources and methods to evaluate the impact of REMS on patient access to REMS drugs and REMS-related administrative burdens to healthcare providers and healthcare systems.

8.6.2. Use scientific methods (social and behavioral) possibly but not exclusively in conjunction with large electronic healthcare data to enhance the understanding of factors (e.g. provider and 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. Advance the science of medication error prevention and analysis

8.6.3.1. Develop artificial intelligence technologies to improve the quality of coded data in medication error reports submitted to the FDA Adverse Event Reporting System (FAERS).

8.6.3.2. Develop and evaluate data mining and other predictive and visual analytical approaches that can be used to identify medication error safety signals in healthcare data.

8.6.3.3. Operationalize natural processing algorithms to identify and extract contributing factors and other information from medication error reports.

8.6.3.4. Development model to integrate medication error information from multiple data sources, including FAERS, published literature, electronic health records, poison control, and social media.

8.6.3.5. Develop methods and evaluate the effectiveness of tall man lettering to distinguish established drug names when used on container labels, electronic drop-down menus, and pharmacy-generated labels.

8.6.3.6. Determine the incidence of medication errors in the United States, public health cost burden, extent of underreporting, and causes of errors.

8.6.3.7. Determine the effectiveness of regulatory actions to prevent errors.

8.6.3.8. Develop methods and evaluate the impact of drug product packaging on 1) prescriber behaviors (e.g., better understand how fixed-quantity packages influence prescribing patterns), and 2) the rates of pediatric accidental exposure.

8.6.3.9. Determine how prescribers make a decision regarding prescribing drug-device combinations such as autoinjectors or inhalers for self- administration to pediatric patients. For example, determine if they assess patients to see if patients can self-administer or provide training specific to pediatric patients.

8.6.3.10. Determine in what user populations or specific disease states training on the use of medical products occurs prior to first use.

8.6.3.11. Assess differences in usability of the same medical product between pediatric and adult populations.

8.7. Informing and Enhancing Audience Understanding Among Diverse Populations

8.7.1. Assess awareness of FDA communications among racial and ethnic minorities and underserved populations (e.g., LGBTQ, rural, elderly), as well as barriers and facilitators to use of FDA's materials.

8.7.2. Identify methods to improve the comprehension and usability of FDA communications, including assessing health literacy, different formats, and amounts of numerical information in FDA communications among those with low health literacy, limited English proficiency, and cultural and language differences.

8.7.3. Conduct studies to determine methods to improve communication strategies among racial and ethnic minorities and underserved populations.

8.7.4. Conduct studies to inform development of FDA communications to racial and ethnic minorities and underserved populations.

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.

9.1.2. Facilitate global access to vaccines and other biological products by building capacity for the infrastructure for the development, delivery and postmarket surveillance

9.1.3. Assess and/or develop surveillance systems for safety and efficacy of vaccines and biologics in low- and middle-income countries (LMIC)

9.1.4. Develop large databases and systems for conducting surveillance and epidemiological studies across a variety of participants from low- and middle-income countries and high-income countries.

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.

9.3 Drug Shortages:

9.3.1 FDA's October 2019 report to Congress, Drug Shortages: Root Causes and Potential Solutions, based on the work of the inter-agency Drug Shortages Task Force recommended efforts to "Create a Shared Understanding of the Impact of Drug Shortages and the Contracting Practices That May Contribute to Them." To implement this recommendation, FDA is interested in working with stakeholders in the health system to develop quantitative estimates of the full impact of drug shortages on areas such as overall costs to the healthcare system and impact on, care provision, and patient outcomes. These estimates could be developed prospectively or retrospectively based on one or many past drug shortages and could be either specific to an organization or projected nationally. Potential areas include developing novel processes, data systems, or methodologies to track, quantify, and communicate the impact of drug shortages, analyzing the impact of past drug shortages on a healthcare provider, closed or integrated health system, payor, or other entity (such as cost and time to provide care, rescheduling of surgeries), assessing the impact of one or more drug shortages on patients, including substitution of alternative therapies, adverse events, and treatment outcomes, or creating a statistical or mathematical model to anticipate the impact of a drug shortage on the health system or patients.

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:

A. 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:

1. 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;
2. Introduction/Background: An introduction covering the purpose and scope of the contract effort;
3. 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;

4. 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.
5. Invoices: Summary of any invoices submitted during the reporting period, including details of any supporting documentation.
6. Action Items: Summary table of activities or tasks to be accomplished by certain date and by whom.
7. Distribution list: A list of persons receiving the Technical Report
8. Attachments: Results on the project are provided as attachments

B. 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.

C. 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:

1. Direct Labor - List individuals by name, title/position, hourly/annual rate, level of effort, and amount claimed.
2. Fringe Benefits - Cite rate and amount
3. Overhead - Cite rate and amount
4. Materials & Supplies - Include detailed breakdown when total amount is over $1,000.
5. Travel - Identify travelers, dates, destination, purpose of trip, and amount. List separately, domestic travel, general scientific meeting travel, and foreign travel.
6. Consultant Fees - Identify individuals and amounts.
7. Subcontracts - Attach subcontractor invoice(s).

8. Equipment - Cite authorization and amount.
9. G&A - Cite rate and amount.
10. Total Cost
11. Fixed Fee (if applicable)
12. 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.

Proposal Stage	Deadline for Submission
Stage 1: Quad Chart and White Paper	**Anytime during open period**
Stage 2: Full Proposal	**Within 30 calendar days of Invitation (unless designated otherwise by the CO)**

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
f. Includes bibliography of any references cited in the White Paper.

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 of the key personnel who will perform the research, highlighting some of their qualifications and experience (Two pages total, not per person).

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-21-00123 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:

1. Single PDF formatted file as an email attachment
2. Page Size: 8 ½ x 11 inches
3. Page limit: 10 pages• Margins – 1 inch
4. Spacing – single
5. 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:
   a. BAA number
   b. Title of proposal
   c. Identity of prime Offeror and complete list of subcontractors, if applicable
   d. Technical contact (name, address, phone/fax, electronic mail address)
   e. Administrative/business contact (name, address, phone/fax, electronic mail address)
   f. 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 (SOW): The SOW should clearly detail the scope and objectives of the effort and the technical approach. The SOW shall clearly identify the specific tasks/aims necessary to complete the scope and objectives of the technical approach. Additionally, the Offeror shall identify whether or not the proposed effort constitutes a non-severable, single, indivisible research study or undertaking, or if the tasks/aims can be separated into severable/stand-alone research deliverables (i.e. pilot study, proof of concept, “go/no-go” decision points in the research, etc.) that may meet a singular and specific need of the Government prior to the completion of the entire proposed research project. If the proposal can be separated into severable deliverables, the Offeror shall identify these points of severability in their SOW and in their budget proposal (see Section C below) as options to be exercised at the discretion of the Government. For example, if Aim 1 can be completed separate and distinct from Aim 2, Aim 1 and its associated tasks shall be proposed as Base Period Tasks, and Aim 2 and its associated tasks would be identified as Option 1 Tasks. Each severable task within the proposal will have its own period of performance and may exceed 12 months if necessary. **Offerors are encouraged to structure their proposals with severable deliverables to the extent it is practicable with the research being proposed as doing so provides the Government with greater flexibility regarding technical needs and funding constraints.

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

8. North American Industry Classification System (NAICS) Code

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 (biographical sketches/resumes are not included in this page limitation) 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.

	Item	Required	Reference
1	Updated Quad Chart	Yes	Attachment 3
2	Protection of Human Subjects	If Applicable	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/Resumes	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 FDA must fully fund non-severable contracts and thus if the proposed effort cannot be broken up into severable/stand-alone deliverables (i.e. pilot study, proof of concept, "go/no-go" decision points in the research, etc.) that meet a need of the Government, then the Offeror shall include the costs of the whole project in the Cost Summary as "Base Period Costs". However, in order to maximize flexibility for funding, Offerors are encouraged to structure the proposed effort into severable/stand-alone deliverables to the extent it is practicable for the research being proposed. The costs per deliverable shall be identified in the Cost Summary as "Base Period Costs" (for the completion of the first severable deliverable) and "Option Costs" (1 Option for each subsequent, severable deliverable). The detailed costs must readily present the costs associated with each specific tasks/aims in the associated WBS and Project Gantt Chart, using the same numbering as provided in the Technical Proposal SOW and should clearly identify whether the costs are associated with "base period costs" or "option costs." The Offeror must also provide a narrative to support the requirements in each cost element.

1.Proposal Cover Sheet: The following information shall be provided on the first page of your pricing proposal:

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.

2. 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. In order to maximize flexibility of funding, the following cost elements shall be provided for each severable task/aim as applicable:

I. Direct Labor- Individual labor category or person, with associated labor hours and

unburdened direct labor rates; Direct salaries are limited in accordance with HHSAR clause 352.231-70 Salary Rate Limitation (December 18, 2015) (see below).

Salary Rate Limitation (December 18, 2015)

(a) The Contractor shall not use contract funds to pay the direct salary of an individual at a rate in excess of the Federal Executive Schedule Level II in effect on the date the funding was obligated.

(b) For purposes of the salary rate limitation, the terms “direct salary,” “salary,” and “institutional base salary,” have the same meaning and are collectively referred to as “direct salary,” in this clause. An individual's direct salary is the annual compensation that the Contractor pays for an individual's direct effort (costs) under the contract. Direct salary excludes any income that an individual may be permitted to earn outside of duties to the Contractor. Direct salary also excludes fringe benefits, overhead, and general and administrative expenses (also referred to as indirect costs or facilities and administrative costs). The salary rate limitation does not restrict the salary that an organization may pay an individual working under a Department of Health and Human Services contract or order; it merely limits the portion of that salary that may be paid with contract funds.

(c) The salary rate limitation also applies to individuals under subcontracts.

(d) If this is a multiple-year contract or order, it may be subject to unilateral modification by the Contracting Officer to ensure that an individual is not paid at a rate that exceeds the salary rate limitation provision established in the HHS appropriations act used to fund this contract.

(e) See the salaries and wages pay tables on the Office of Personnel Management website for Federal Executive Schedule salary levels.

II. Indirect Costs – Fringe Benefits, Overhead, G&A, etc. – Offerors shall provide the applicable indirect rates and the cost bases for those rates. Offerors shall provide documentation of negotiated indirect rates agreements to the extent they have been audited and/or approved by their cognizant agency. If applicable, the offeror shall also provide the name and POC for the cognizant agency that established the rate agreement. Offerors subject to OMB Uniform Guidance 2 CFR 200 may propose a de minimis 10% indirect rates in accordance with 2 CFR 200.414(f), if they do not already have a negotiated indirect 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. **NOTE: A Subcontracting Plan is required as an Appendix to the Cost Proposal if the cost of the proposed research is expected to exceed $750K (See FAR 19.704).**

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.

i. Fee/profit including percentages.
ii. 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.

	Item	Required	Reference
1	DUNS, TIN and NAICS	Yes	
2	Representation and Certifications	Yes	FAR 4.1201
3	HHS Small Business Subcontracting Plan	If Applicable (over $750,000.00 and not a small business)	Template Provided as Separate Attachment to Announcement
4	Summary of Related Activities	Yes	Attachment 1
5	Disclosure of Lobbying Activities	If Applicable	FAR 52.203-11
6	Report of Government Owned, Contractor Held Property	If Applicable	http://oamp.od.nih.gov/sites/default/files/DGS/contracting-forms/Govt-Owned-Prop.pdf

E. Representation and Certifications:

Prospective contractors shall complete electronic annual representations and certifications at SAM accessed via 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.

More specifically, the FDA human Protection Review process is described below:

Human Subject Protection Review

For research exempt from the requirements of 45 CFR Part 46:

(a) The Contractor will submit to FDA a letter from their IRB or human subject protection entity that the proposed research is exempt (see 45 CFR 46.104).

(b) In accordance with SMG 9001.4, FDA will follow its procedures for exempt research determination. Data collection from human subjects cannot commence under this contract until the FDA COR provides the Contractor with the outcome of the FDA determination.

For nonexempt human subjects research:

(a) The Contractor agrees to protect the rights and welfare of human subjects involved in research under this contract by complying with 45 CFR Part 46 and the clause at HHSAR 352.270-4b.

(b) Initial proof of compliance with 45 CFR Part 46 shall consist of:

(1) A copy of a current Federal-wide Assurance on file with OHRP (https://www.hhs.gov/ohrp/ federalwide-assurances-fwas.html). The copy of a current Federal–wide Assurance shall be included with the Contractor's proposal;

(2) A letter from the Contractor's local IRB (the Institutional Review Board (IRB) specified in the Offeror's Assurance of Compliance) stating that it has reviewed and approved the proposed research protocol. The letter from the local IRB shall be submitted to the Contracting Officer Representative (COR).

(3) In accordance with SMG 9001.4, the FDA will determine if FDA is considered engaged in the research for purposes of 45 CFR part 46. Data collection from human subjects cannot commence under this contract until the FDA COR provides the Contractor with the outcome of the FDA determination. When that determination is made, the FDA will confirm the extent to which the terms of "352.270-11 Protection of Human Subjects—Research Involving Human Subjects Committee (RIHSC) Approval of Research Protocols Required" apply.

As described above, there are certain provisions regarding when agencies within HHS, including FDA, may be 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)

(a) The Department of Health and Human Services (HHS) regulations for the protection of human subjects, 45 CFR part 46, are available on the Office for Human Research Protections (OHRP) website at: http://www.hhs.gov/ohrp/index.html.

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).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.

(f) 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.

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

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

(b) 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.

(c) 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 Service'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 legislature 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, excludingpeer-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.

M. CONFLICT OF INTEREST

As a regulatory agency charged with protection of public health, the Food and Drug Administration (FDA) must maintain public confidence in the integrity of its decisions. The FDA has policies and procedures that safeguard against actual and apparent conflict of interest on the part of its employees. In contracting for review and evaluation of scientific data and information submitted to the agency, it is critical that the FDA be assured that there is no actual or apparent conflict of interest on the part of the individual contractor. Offers performing work under this contract must assure the protection of information and data they receive under this contract from unauthorized use or disclosure, and must avoid actions that would cause a reasonable person to question the impartiality of the contractor.

(a) Purpose. The purpose of this clause is to ensure that the contractor and its subcontractors:

(1) Are not biased because of their financial, contractual, organizational, or other interests which relate to the work under this contract, and

(2) Do not obtain any unfair competitive advantage over other parties by virtue of their performance of this contract.

(b) Scope. The restrictions described herein shall apply to performance or participation by the contractor, its parents, affiliates, divisions and subsidiaries, and successors in interest (hereinafter collectively referred to as “contractor”) in the activities covered by this clause as a prime contractor, subcontractor, co-sponsor, joint venturer, consultant, or in any similar capacity. For the purpose of this clause, affiliation occurs when a business concern is controlled by or has the power to control another or when a third party has the power to control both.

(c) Warrant and Disclosure. The warrant and disclosure requirements of this paragraph apply with full force to both the contractor and all subcontractors. The contractor warrants that, to the best of the contractor's knowledge and belief, there are no relevant facts or circumstances which would give rise to an organizational conflict of interest, as defined in FAR Subpart 9.5, and that the contractor has disclosed all relevant information regarding any actual or potential conflict. The contractor agrees it shall make an immediate and full disclosure, in writing, to the Contracting Officer of any potential or actual organizational conflict of interest or the existence of any facts that may cause a reasonably prudent person to question the contractor's impartiality because of the appearance or existence of bias or an unfair competitive advantage. Such disclosure shall include a description of the actions the contractor has taken or proposes to take in order to avoid, neutralize, or mitigate any resulting conflict of interest.

(d) Remedies. The Contracting Officer may terminate this contract for convenience, in whole or in part, if the Contracting Officer deems such termination necessary to avoid, neutralize or mitigate an actual or apparent organizational conflict of interest. If the contractor fails to disclose facts pertaining to the existence of a potential or actual organizational conflict of interest or misrepresents relevant information to the Contracting Officer, the Government may terminate the contract for default, suspend or debar the contractor from Government contracting, or pursue such other remedies as may be permitted by law or this contract.

(e) Subcontracts. The contractor shall include a clause substantially similar to this clause, including paragraphs (f) and (g), in any subcontract or consultant agreement at any tier expected to exceed

the simplified acquisition threshold. The terms “contract,” “contractor,” and “Contracting Officer” shall be appropriately modified to preserve the Government's rights.

(f) Prime Contractor Responsibilities. The contractor shall obtain from its subcontractors or consultants the disclosure required in FAR Part 9.507-1, and shall determine in writing whether the interests disclosed present an actual, or significant potential for, an organizational conflict of interest. The contractor shall identify and avoid, neutralize, or mitigate any subcontractor organizational conflict prior to award of the contract to the satisfaction of the Contracting Officer. If the subcontractor's organizational conflict cannot be avoided, neutralized, or mitigated, the contractor must obtain the written approval of the Contracting Officer prior to entering into the subcontract. If the contractor becomes aware of a subcontractor's potential or actual organizational conflict of interest after contract award, the contractor agrees that the Contractor may be required to eliminate the subcontractor from its team, at the contractor's own risk.

(g) Waiver. The parties recognize that this clause has potential effects which will survive the performance of this contract and that it is impossible to foresee each circumstance to which it might be applied in the future. Accordingly, the contractor may at any time seek a waiver from the Head of the Contracting Activity by submitting such waiver request to the Contracting Officer, including a full written description of the requested waiver and the reasons in support thereof.

Section 5: Full Proposal Submission

Full Proposals must be emailed to FDABAA@FDA.HHS.GOV by the date specified in the invitation letter. Emails to the FDABAA inbox shall not exceed 20 MBs.

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 proposed award.

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

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 a two-tier evaluation of each Offeror's Quad Chart and White Paper (Stage 1) and Full Proposal (Stage II). After receiving an Offerors' Quad Chart and White Paper Submission, the FDA will conduct a High-Level review to determine potential program relevance. If the submission is determined to have the potential to align with an Agency Program, the Quad Chart and White Paper will be forwarded for a full Stage I Evaluation. Both Stage I proposals and Stage II proposals (for Stage I Offerors invited to submit full proposals) 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.
- Ownership of the Intellectual Property.

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.

1. 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.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

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

2. 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*****.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

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

3. 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.

Name	Title/Position	Total Proposed Effort
1.		
2.		

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.

(a) 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.

(b) 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

A. 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. Description of Effort: A bullet list (2-3) of the primary scientific challenges being addressed	Picture or Graphic that illustrates the research or concept (e.g. data figures, molecule illustrations of processes)

Benefits of Proposed Technology: Challenges: Research and Development Justification:	Bullet list of the major goals/milestones by Project Year Proposed Funding: Base period cost plus each option period (no more than 5 years total) **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 Offerors 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).