FDABAA-24-00123

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 and Small Businesses are strongly encouraged to respond. Offerors may include single entities or teams from private sector organizations, Federally Funded Research and Development Centers (FFRDCs) (see page 5 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 Only [Not Grants]

Notes: ***Regarding Funding***

To ensure sufficient time to conduct the two-tiered evaluation described in Section I and still be considered for an award within the current fiscal year, prospective Offerors are strongly encouraged/ required to submit Stage One Submittal Packages with:

1. Checklist following required template (See attachment 3)

2. Freestanding Concept Paper following required template (See attachment 4)

3. Freestanding Full Proposal following required template

Concept Papers and Full Proposal shall be submitted no later than 11:59 pm, Eastern Standard Time, February 19, 2024, and earlier if possible. A submission will be considered incomplete if any of these critical elements are missing. Stage One Submittal Packages received after that date will still be accepted, but due to a lack of lead time, will not be considered for award in FY24.

Notice and Disclosure Regarding Incomplete/Nonconforming Stage One Submittal Packages: All Stage One Submittal Packages received in response to this announcement must be complete and comply with all instructions provided herein (Note: Part III: Proposal Preparation and Submission must be considered; it lays out the details of what is included in Stage I and Stage II package). The FDA reserves the right to reject (or otherwise give no further consideration to) any packages that are found to be (1) missing any pertinent information, (2) submitted in a nonconforming format, or (3) otherwise require exchanges with offerors for the FDA to complete its evaluation due to patent or latent ambiguities contained within the submittal.

Contents

INTRODUCTION

Advancing Regulatory Science and Innovation

This Broad Agency Announcement (BAA), which sets forth research areas of interest for FDA, 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 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.

In the US, FDA-regulated products account for about 20 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, biologics, 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 in the regulatory science framework and further described in Part I of this announcement. The goal of this regulatory science framework is to ***harness regulatory science*** research to accomplish the following **three charges** that directly align with FDA's mission, to:

I. Modernize development and evaluation of FDA-regulated products
II. Strengthen post-market surveillance and labeling of FDA-regulated products
III. Invigorate public health preparedness and response of the FDA, patients, and consumers

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. This BAA is available on www.beta.sam.gov using Keyword Search "FDABAA-24-00123."

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 on the same site when they occur. Interested parties are encouraged to periodically check the website for updates and amendments. Potential dates for posting amendments to this

announcement are 10/13/2023; 10/27/2023; 11/10/2023; 11/24/2023; 12/8/2023; 12/22/2023; and/or 1/12/2024

Save the date for the 2023 FDA Broad Agency Announcement (BAA) Day! October 25, 2023. BAA Day for 2023 will be hosted on October 25th, 2023, as a virtual only event and will provide an opportunity to learn more about the application process and FDA's priorities for regulatory research.

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. The FDA will be giving preference to proposals that use a cost reimbursement model vice a firm fixed price model. Research, by definition, does not always produce a deliverable, whether due to the nature of the research or the results of the research. By proposing a severable, cost reimbursable contract, risk is reduced to both the government and the awardee. In the future, the FDA may move to only utilizing a cost type model for this BAA award.

5. Please note, the contract requirements differ between commercial and educational entities. It is HIGHLY recommended that all potential proposal submitters review Part 31 - Contract Cost Principles and Procedures:

31.103 Contracts with commercial organizations.

31.104 Contracts with educational institutions.

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 (See Table 1, which highlights the topic areas that are priorities for FDA for FY 24). This section presents the technical objectives that FDA seeks to achieve through this BAA. Offerors should propose a Statement of Work (SOW) that is consistent with research and development work as defined in FAR 35.001. Proposal preparation and submission instructions are contained in Part III.

	FDA-Regulated Areas						*Demographics & Populations*			
Table 1: Areas of regulatory science research priority for FDA in FY 24. For each charge (rows), the "x" marks priority areas for relevant FDA regulated product areas, and demographics & populations (columns).	Cross-cutting	Biologics	Biosimilars	Devices	Drugs	Tobacco Products	*Racial and Ethnic*	*Women*	*Persons with Rare Diseases*	*Persons with cancers*
I. Modernize development and evaluation of FDA-regulated products										
A. Alternative Methods	X		X			X		X	X	
B. Advanced Manufacturing Approaches	X	X		X	X					X
C. Analytical and Computational Methods	X	X	X	X	X	X	X	X	X	X
D. Biomarkers	X				X	X		X	X	X
E. Clinical Outcome Assessment (COA)				X	X		X	X		X
F. Complex and Novel Clinical Trial Design				X	X	X	X	X	X	X
G. Predictive Toxicology	X				X	X		X		X
H. Methods for Assessing Be havioral, Economic, or Human Factors				X	X	X				
I. Approaches to Incorporate Patient and Consumer Input	X									
J. Methods to Assess Real-World Data to serve as Real-World Evidence	X	X	X			X		X	X	X
K. Methods to Assess Data Source Interoperability	X									
II. Strengthen post-market surveillance and labeling of FDA-regulated products										
A. Methods to Assess Real-World Data to Support Regulatory Decision-Making	X			X	X			X		X
B. Using and Validating Artificial Intelligence Approaches	X			X	X			X		
C. Novel Clinical Trial Design, Statistical and Epidemiologic Methods	X									X
D. Automated Reporting Tools for Adverse Events and Active Surveillance	X	X			X					X
E. Methods to Improve Communication About Risk to Patients and Consumers				X	X	X		X		
F. Approach to Expand Data Capacity, and Increase Data Quality and Use	X				X		X			
G. Efforts to Harmonize Existing and Emerging Data Standards	X									
III. Invigorate public health preparedness and response of the FDA, patients, and consumers										
A. Reinforce Medical Countermeasures Initiative to Increase Preparedness and Response for Emerging Public Health Threats				X			X	X	X	
B. Antimicrobial Resistance					X					
C. Patient and Consumer Engagement	X				X		X			
D. Substance Use and Misuse				X	X	X	X			
E. One Health Approaches	X									
F. Strengthen Global Product Safety Net	X	X			X					
G. Emerging Technologies				X						

Because resources are limited, preference will be given to projects geared toward advancing **regulatory science**, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of **FDA-regulated products**, which include medical devices, drugs, biologics, combination products, veterinary medicine, food, cosmetics, dietary supplements, and tobacco products.

In addition to the product areas that FDA regulates, FDA aims to target innovation in regulatory science that advances the health of the following **demographic groups and populations**, some of which have clinical characteristics that may frequently preclude their participation in clinical research or bear disproportionate burden of tobacco product risk and harm: racial & ethnic minority populations, women's health, persons with cancer and persons with rare diseases (including rare cancers).

The three charges are foundational to FDA's mission, and thus are not expected to change. We have designated areas to target regulatory science efforts that support the FDA's mission for each charge. The areas of regulatory science are designed to change with the evolution of science, technologies, and public health needs. Moreover, each area has been designated under a specific charge, and where possible, specific product areas and/or demographics and populations have been labeled. When multiple product areas and/or demographics and populations have been identified for a given regulatory science area, we use the term ***cross-cutting*** in place of the specific product area and/or demographic or population. Through collaborative interactions with stakeholders, we aim to foster robust and innovative approaches to advance regulatory science through the following framework.

Charge I: Modernize development and evaluation of FDA-regulated products

- **A.** Alternative Methods
- **B.** Advanced Manufacturing Approaches
- **C.** Analytical and Computational Methods
- **D.** Biomarkers
- **E.** Clinical Outcome Assessment
- **F.** Complex and Novel Clinical Trial Design
- **G.** Predictive Toxicology
- **H.** Methods for Assessing Behavioral, Economic, or Human Factors
- **I.** Approaches to Incorporate Patient and Consumer Input
- **J.** Methods to Assess Real-World Data (RWD) to serve as Real-World Evidence (RWE)
- **K.** Methods to Assess Data Source Interoperability

Charge II: Strengthen post-market surveillance and labeling of FDA-regulated products

- **A.** Methods to Assess Real-World Data to Support Regulatory Decision-Making
- **B.** Using and Validating Artificial Intelligence Approaches
- **C.** Novel Clinical Trial Design, Statistical and Epidemiologic Methods
- **D.** Automated Reporting Tools for Adverse Events and Active Surveillance

E. Methods to Improve Communication About Risk to Patients and Consumers
F. Approach to Expand Data Capacity, and Increase Data Quality and Use
G. Efforts to Harmonize Existing and Emerging Data Standards

Charge III: Invigorate public health preparedness and response of the FDA, patients, and consumers

A. Reinforce Medical Countermeasures Initiative (MCMi)
B. Antimicrobial Resistance
C. Patient and Consumer Engagement
D. Substance Use and Misuse
E. One Health Approaches
F. Global Product Safety net
G. Emerging Technologies

Additional information regarding specific FDA initiatives, and/or center and office priorities can be found in the Part I Appendix.

I. Modernize development and evaluation of FDA-regulated products

The following focus areas of regulatory science are identified to accomplish Charge I, *modernize development and evaluation of FDA-regulated products*:

A. Alternative Methods

Examples: Novel in vitro, in vivo, and in silico methods; Microphysiological Systems (MPS); Organ-on-a-chip; Complex In Vitro Models (CIVM); Use of alternative assays

1. *Cross-cutting*
   a. Integrate an understanding of product quality and safety based on novel genomic, proteomic, metabolomic, and other-OMIC technologies.
   b. Develop and use microphysiological systems (MPS), complex in vitro models (CIVM), and computational modeling approaches to improve predictivity of nonclinical testing and potentially address the 3Rs (replace, reduce, and refine) of animal use in product testing and scientific research.

2. *Biosimilars*
   a. Improve the efficiency of Biosimilar product development
   b. Investigate and evaluate informative, scientifically appropriate methodologies to predict immunogenicity by advancing the knowledge of analytical (including physical, chemical, and biological function assays), pharmacological and clinical correlations as it relates to biosimilarity.

3. *Rare diseases*
    a. Develop new alternate methods (MPS and CIVM) to support regulatory submissions demonstrating efficacy and safety assessment of drugs for rare diseases.

4. *Tobacco*
    a. 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., differentiated primary lung cells grown at an air liquid interface or lung-on-a-chip and MPS model);
        i. Predict threshold of toxicological concerns resulting from exposure to Electronic Nicotine Delivery Systems (ENDS) aerosols and/or their constituents.
        ii. Predict levels of tobacco-related toxicants resulting from exposure to ENDS aerosols and/or their constituents that induce in vitro responses to in vivo exposure levels that could result in human or animal adverse effects.
        iii. Feasibility evaluation of quantitative data analysis methods designed to assess the relative mutagenicity/genotoxicity potencies (using Ames assay, micronucleus assay, or other standard OECD approved genotoxicity assays) of chemical mixtures and individual entities commonly found in ENDS aerosols for which there are limited or no carcinogenicity data via the inhalation route (such as, but not limited to, ethyl maltol, benzaldehyde, veratryl aldehyde, maltol, d,l-isomenthone, furan, furfurals, diacetyl, bisphenol A, chloroform, phthalate; and heavy metals such as, but not limited to, nickel (Ni), chromium (Cr), cadmium (Cd), iron (Fe), and lead (Pb)).
        Methods that are robust and amenable are of interest. Of particular interest is (1) whether such relative mutagenicity/genotoxicity potency approaches could assess possible additive, synergistic, or antagonistic responses between different mutagens/genotoxins in mixtures and (2) if calculated mutagenicity/genotoxicity potencies can predict known relative cancer potencies identified in carcinogenicity studies.

5. *Women's Health*
    a. Develop alternative methods in support of development of diagnostics and therapeutics targeting women, including, but not limited to:
        i. Methods to evaluate innovative, new devices and diagnostics specifically designed for use in women.
        ii. Methods to enhance the evaluation of devices used in both men and women to take into consideration sex differences like organ

size/anatomy/ physiology/human factors differences that may affect device performance.

iii. Foster development methods to evaluate sex-matched devices and companion diagnostics.

b. Develop methods to evaluate FDA regulated-product safety and effectiveness during pregnancy and lactation.

B. Advanced Manufacturing Approaches

Examples: New medical product manufacturing technologies and processes that can improve quality of FDA-regulated products, address shortages of medicines, and/or speed time-to-market; Technologies may include Continuous, Additive and Smart manufacturing

1. Cross-cutting

a. Facilitate development and evaluation of:
   i. Automated or semi-automated in-process monitoring and control systems and methods.
   ii. Test and validation metrics for advanced manufacturing processes including additive manufacturing, integration and intensification of process unit operations, adaptive processes, and automation of operations.
   iii. New ways to evaluate gene and cell therapy products and their manufacturing methods
   iv. How implementation of digital technologies, remote monitoring, and data are fed back into product design, development, and life cycle risk management impacts the control, responsiveness, and product quality.

b. Investigate the effect of advanced manufacturing on product quality:
   i. Examine specific novel material and manufacturing technologies to determine how they impact product failure rates;
   ii. Research focuses on technologies and materials that result in manufacturing technology, tools, or approaches that enhance control of critical quality attributes of medical products and key inputs, including drug substances, products, or medical devices.
   iii. Improve manufacturing capabilities for devices, complex drugs, and biologics.

c. 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:
   i. Supply chain resilience to disruption,

ii. Supply chain visibility, monitoring, and data sharing processes and platforms,

iii. Personalization,

iv. Decreased reliance on foreign supply chains.

d. 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.

e. Investigate or develop methods to increase implementation and adoption of advanced manufacturing methods in critical areas that impact production of vaccines, diagnostics, critical medicines and devices, and potential shortage products. This may include demonstrations of the value proposition and advantages of implementing advanced manufacturing and processes to patient access, economics, efficiency, and increased supply chair resilience

2. *Biologics*
   a. Explore novel applications of advanced (e.g., integrated and continuous) manufacturing processes for complex biologic products, such as vaccines, tissue-engineered products, and cell and gene therapies. Describe the potential impact of the proposed enabling technology on process control strategy and its readiness for broad implementation in the biopharmaceutical industry. Topics may include but are not limited to:
      i. Closed and automated manufacturing processes,
      ii. Modular manufacturing platforms with integrated in-process testing capabilities,
      iii. Manufacturing process modeling and simulation,
      iv. Advanced or novel process analytical technologies for real time process control and release,
      v. Improved cell lines and improved upstream cell culture production processes for vaccine antigen or viral vector manufacturing.
   b. Develop new approaches such as *in vitro* and *in vivo* methods to identify measurable characteristics of product safety, quality, and potency when evaluating new biotherapeutics (e.g., engineered

tissues or cell therapy products, including stem cell- derived products), for clinical application in regenerative medicine;

i. Identification of critical quality attributes (CQAs) and development of advanced assays for characterization of CQAs in products for gene and cell therapies,
ii. Development of reference materials and standards for gene and cell therapies.

3. *Devices*
   a. Develop novel materials intended for use as materials of construction or manufacturing aids for medical devices;
      i. Advance the development of novel materials for manufacturing of respirators and other personal protective equipment including the development of integrated virocidal or other infection control blocking capabilities.
   b. Develop standardized methods for devices to dynamically update their data dictionary and related embedded software to respond to new data needs, such as those driven by public health response to emerging threats
   c. Develop improved methods and tools for the validation and lifecycle maintenance of digital technologies supporting Industry 4.0 for device manufacturing, including data capture and storage, adaptive process control, digital twins, and internet of things.

4. *Drugs*

   a. Develop improved methods and tools for the validation and lifecycle maintenance of digital technologies for Industry 4.0 for pharmaceutical manufacturing including novel sensors, data management, adaptive process control, digital twins, and cybersecurity.
   b. Develop improved methods for the manufacturing of sterile drug products including rapid monitoring for the detection of microbial contamination.

5. *Medical Countermeasure Initiative (MCMi)*
   a. 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 process analytical technologies).
   b. Advance broadly applicable, commercially ready (pilot ready or commercially implementable: MRL 4-6 and 7-9 respectively) 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.

6. *Neo-antigen-based therapies, Oncology*
    a. Create novel technologies and approaches to evaluate both efficacy and safety for neoantigen-based therapies that incorporate unique features of individual cancers, neoantigen and antigen targets, and neoantigen and immune responses. Examples may include neoantigen-based vaccines, redirecting T-cell specificity by genetically modifying T cells with receptors specific against neoantigen-derived epitopes.

7. *Pediatric Oncology:*
    a. 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.

C. Analytical and Computational Methods

Examples: Development and use of computational methods and in-silico modeling; Simulation-based approaches; Advanced quantitative methods-based modeling; Predictive Analytics such as Predictive modeling, Model-informed drug or device development; Artificial Intelligence and Machine Learning

1. *Cross-cutting*

    a. 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:
        i. Generative Design
        ii. Production simulation and simulated process validation,
        iii. AI/ML application to quality system activities, such as, complaint management, trending, or others,
        iv. Intelligent Design Control
        v. Closed loop risk-management.

    b. Develop computer models of cells, organs, and systems (including the impact of hormones) to predict product risk, safety and efficacy of
        i. FDA regulated products

ii. ingredients in dietary supplements, including potential interactions with drugs and other dietary supplements.

c. 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.
d. Develop and apply data mining, knowledge building, and data visualization tools to inform computer model development, clinical risk prediction, and regulatory decision-making;
e. Develop novel methods to display model output in both graphical and numeric formats;
f. Explore the role of digital health technologies in the evaluation of new medical products;
g. 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.
h. Develop clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes.

2. *Biologics*
   a. Develop computational tools and models to predict immunogenicity for biologic products including modified sequences for mitigation of immunogenicity risk.

3. Biosimilars

Improving the efficiency of biosimilar product development

   a. Review and evaluate opportunities for streamlining and targeting biosimilar product development in consideration of scientific advancements in analytical (including physical, chemical, and biological function assays), and pharmacological assessments and experience with prior biosimilar product development and marketed biosimilar products.

4. *Devices*
   a. Develop computational modeling and simulation methods to promote the use of in-silico assessment of devices and materials, especially for pediatric and special populations.
   b. Evaluate the use of computational modeling and simulation to improve or optimize device sterilization processes. Explore validation requirements and methods to enable the use of the modeling and simulation data as a valid source of digital evidence.

5. *Drugs*
    a. Develop and evaluate the use AI and hybrid mechanistic AI models in drug manufacturing including model validation, transparency of model outputs, and model lifecycle maintenance. For more information see the Artificial Intelligence in Drug Manufacturing discussion paper

    b. Advance methodologies to generate clinical evidence using AI/ML sufficient to support regulatory use:
        i. Demonstrate how clinical evidence generated from the use of AI/ML could inform clinical studies for regulatory use
        ii. Develop and validate tools and models that assess fitness of AI/ML use to support regulatory decision making (e.g., using a placebo digital twin)
        iii. Develop and validate methods to predict medical product performance using AI/ML,
        iv. Evaluate ML methods with a focus on identifying and/or addressing sources of (methodological) bias
        v. Advance causal AI inference

    c. Develop Methods for Generics to Address Harmful Impurities such as Nitrosamines:
    This research area focuses on understanding how ingredients in generic drug products may either contribute to or mitigate the formation of harmful impurities such as nitrosamine adducts, including nitrosamine drug substance related impurities (NDSRIs), evaluating the risk of human exposure to these impurities, and developing methods for abbreviated new drug application (ANDA) applicants to efficiently address the potential risks. For more information, see the Generic Drug User Fee Amendments (GDUFA) science and research priority initiatives for fiscal year (FY).

    d. Enhance the Efficiency of Equivalence Approaches for Complex Active Ingredients:
    This research area focuses on improving advanced orthogonal methods for the characterization of chemical compositions, molecular structures, and distributions of complex active ingredients and associated impurity profiles that can elucidate attributes of complex active ingredients and support immunogenicity risk assessments that may be critical to their performance and, thereby, support the development of efficient characterization-based bioequivalence (BE) and pharmaceutical equivalence (PE) approaches. For more

information, see the GDUFA science and research priority initiatives for FY.

e. Enhance the Efficiency of BE Approaches for Complex Dosage Forms and Formulations:
This research area focuses on improving efficient characterization-based (in vitro) BE approaches for complex dosage forms by identifying relevant critical quality attributes (CQAs) to characterize, and suitable test methods for doing so. For more information, see the GDUFA science and research priority initiatives for FY.

f. Enhance the Efficiency of BE Approaches for Complex Routes of Delivery:
This research area focuses on understanding of how ingredients and other aspects of a formulation influence drug absorption via complex routes of delivery, building in vivo predictive models and identifying corresponding failure modes for BE, to support the development of efficient BE approaches for these products. For more information, see the GDUFA science and research priority initiatives for FY.

g. Enhance the Efficiency of Equivalence Approaches for Complex Drug-Device Combination Products:
This research area focuses on evaluating the impact of identified differences in the user-interfaces, hardware, software or propellants between a prospective generic and the reference listed drug on the BE, therapeutic equivalence or post-marketing safety of generic drug-device combination products. For more information, see the GDUFA science and research priority initiatives for FY.

h. Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products:
This research area focuses on understanding of how ingredients in oral and parenteral drug products may modulate bioavailability, and on improving biorelevant dissolution methods as well as in silico models to support the expansion of biowaivers and to support global harmonization under ICH M13A. This includes developing evidence to support the feasibility of biowaivers for immediate release (IR) oral drug products with differences in formulations larger than currently recommended in FDA guidance, or for IR oral drug products that do not demonstrate comparable dissolution profiles across strengths. It also includes establishing approaches to manage potential risks related to subject safety more consistently when developing clinical BE study recommendations and elucidating potential failure modes for BE with special populations (e.g., pediatric or geriatric patients) to

improve tools and methodologies that can be incorporated into BE study recommendations which ensure the equivalence of therapeutic outcomes in diverse populations. For more information, see the GDUFA science and research priority initiatives for FY.

i. Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of BE:
This research area focuses on developing tools and advancing approaches to integrate complementary in silico (modeling), in vivo, and in vitro evidence in ways that collectively mitigate the risk of failure modes for BE and support a framework for virtual BE studies. For example, while it may not be feasible to adequately characterize the long-term bioavailability of drugs from for long-acting injectable, insertable or implantable (collectively, LAI) products using in vivo or in vitro methods alone, it may be feasible to integrate limited in vivo and in vitro data with PBPK models that generate the remaining evidence needed to support a demonstration of BE. This area includes research on the use of MIE to evaluate failure modes for BE and to optimize the design of BE studies. For more information, see the GDUFA science and research priority initiatives for FY.

j. Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools:
This research area focuses on building systems and infrastructure that support the functionality of AI/ML tools which FDA can use to improve the efficiency and consistency of scientific assessments and advice. This includes using AI/ML tools such as natural language processing (NLP) that automate the assembly of key information routinely assessed during the development of recommendations in Product Specific Guidelines (PSGs), or during the assessment of ANDAs, as well as AI/ML tools that facilitate planning and resource allocation to support GDUFA commitments. For more information, see the GDUFA science and research priority initiatives for FY.

6. *Immuno-Oncology*
   a. Perform analyses of clinical data to develop a better understanding of the proportion of patients with atypical response and/or resistance and explore the development of predictive analytics related to ICI treatment and resistance.

7. *Neo-antigen-based therapies, Oncology*
   a. Develop, optimize, and standardize bioinformatic algorithms for neoantigen identification and development of personalized therapies.

These are important to ensure the efficacy and safety of these products in the treatment of patients with cancer.

8. *Precision Oncology*
   a. Develop novel selection/response biomarkers using algorithms combining different types of medical images including radiology images (e.g., CT, PET) and/or histopathology images combined with novel analysis approaches such radiomics and artificial intelligence/machine learning.

9. *Rare Cancers, Oncology*
   a. Investigations using text mining and artificial intelligence to analyze, assess and interpret the scientific literature and other public databases of genomic and transcriptomic analyses in rare cancers to identify drugs that have been used against molecular targets relevant in rare cancers.
   b. Investigations to characterize the plasma membrane surface-ome of health cells/tissues and ultra-rare tumors such that logic gated CAR-T cell therapeutic approaches can be encouraged, and potential on-target, off-tumor safety issues can be identified

10. *Racial and Ethnic Minority Health*
    a. Examine the distinctive health characteristics and attributes of racial and/or ethnic minority populations 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.

11. *Women's health*
    a. Develop methods to evaluate sex differences in the safety and efficacy of FDA regulated products.
    b. Develop novel tools to evaluate regulated-product toxicity or the safety and efficacy during pregnancy and lactation.

12. *Rare disease*
    a. 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 populations (e.g., pediatrics) and heterogeneity of patients with rare conditions.

13. *Tobacco*

a. Develop innovative models for effectively extrapolating in vitro exposure levels that cause toxicological response to in vivo adverse effects for the assessment of human health risk resulting from exposure to ENDS and/or their constituents.
b. Understand the potential or actual impact of FDA regulatory actions. Priorities for impact analysis include: behavioral economics experiments and modeling (e.g., population modeling, agent-based modeling) studies to estimate the range of potential impacts on behavior and health of potential FDA regulatory actions such as product standards addressing toxicity, appeal, and addiction (e.g., prohibiting flavored cigars other than tobacco flavored, prohibiting menthol as a characterizing flavor in cigarettes and cigars, lowering the nicotine content in combustible cigarettes); and where appropriate to the research question, studies involving populations with disproportionate burden of tobacco product risk and harm are encouraged.
c. Develop new modeling approaches to assess the risk of new tobacco products (e.g., non-tobacco nicotine products) that will potentially enter the market by considering how such products may affect users and non-users of the product based on factors including, but not limited to exposure to toxicants, product characteristics and demographic attributes of the users and usage patterns.
d. Develop new modeling approaches to characterize exposures that reflect long-term non-continuous tobacco product inhalation exposures from use of ENDS or heated tobacco products as well as dual use with conventional cigarettes. Inhaled tobacco product exposure assessment would ideally consider the following modeling parameters:
    i. Concentration of chemicals in the smoke or aerosol, or in the tobacco product itself (e.g., e-liquid, tobacco filler),
    ii. Puff topography (e.g., sessions per day, puffs per session, puff volume, inter-puff interval),
    iii. Tobacco product intake rate (e.g., volume of e-liquid used per day, cigarettes smoked per day),
    iv. Exposure frequency (e.g., daily, one day per week, five days per month),
    v. Exposure duration – How long a person has been using the tobacco product of interest (in years),
    vi. Averaging time – Lifespan for a given population,
    vii. Transitions between different tobacco products used in a lifetime,
    viii. Potential use of single or multiple tobacco products in the same timeframe (e.g., exclusive, dual, or poly-use),
    ix. Transitions between tobacco use and no tobacco use in a lifetime,

x. Potentially different effects of tobacco use earlier in life versus later in life.

D. Biomarkers

Examples (includes imaging): Biomarker identification; Biomarker qualification; Biomarker evaluation, Biomarker validation

1. Cross-cutting

a. Advance methodologies for qualification of biomarkers and to support analytical and clinical validation of biomarkers that can provide objective measures to replace or compliment subjective classifications of disease diagnosis or progression.
b. Advance biomarker and clinical tool validation to reduce disease heterogeneity in clinical trials by refining clinical disease classification or inform reproducible patient stratification based on risk factors in therapeutic areas with unmet need.
c. 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.
d. Evaluate the biomarkers and the role of the microbiome in contributing to adverse responses through alterations in metabolism or other mechanisms, especially in pediatrics, and the associated long-term health impact.
e. Evaluate strategies for validation of innovative biomarkers or clinical tools that offer a sensitive and specific reflection of the pathophysiologic state for progressive diseases with unmet need.
f. Investigate precision medicine and biomarkers for predicting medical device performance, disease diagnosis and progression.
g. Demonstrate how terminology for encoding biomarkers in real-world data can integrate with patient care data encoding standards recommended by the Office of the National Coordinator (SNOMED, LOINC, and RxNorm).
h. 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. *Drugs*

a. Evaluate strategies for assessment of innovative non-biomarker drug development tools that offer a sensitive and specific reflection of pathology or treatment responses.

3. *Immuno-Oncology*

   a. Develop biomarkers and/or pharmacodynamic endpoints to demonstrate the effect of ICI in cancer immunotherapies or as part of a combination regimen in treatment-naïve and immuno-therapy resistance settings.

   b. 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.

4. *Precision Oncology*

   a. Identify and explore approaches to validate biomarkers (including liquid biopsy biomarkers) for escalation/de-escalation of treatments in the neoadjuvant, adjuvant or advanced disease settings;
   b. Conduct studies to compare the analytical and clinical performance of local and centralized molecular tests used for patient enrollment on cancer clinical trials;
   c. 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;
   d. 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. A particular area of interest is to improve understanding of any differences in activity of PARP inhibitors in patients with BRCA mutations vs. other individual homologous recombination repair (HRR) mutations.

5. *Pediatric Oncology*

   a. Development of preclinical models (e.g., patient-derived xenograft models, orthotopic mouse models, organoids) of pediatric tumors to facilitate decision-making regarding the evaluation of emerging novel agents potentially applicable to tumors which predominantly occur in the pediatric population;
   b. Investigations 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 to: (1) identify drugs that have been used against molecular targets relevant in pediatric cancers and/or (2) elucidate the relevance of specific molecular targets to the growth and/or progression of pediatric tumors to understand and assess target actionability.

6. *Health equity and special populations, Oncology*
    a. Characterize the prevalence of currently druggable biomarkers in racial/ethnic minorities and assess implications for enrollment in clinical trials.

7. *Rare Cancers, Oncology*
    a. 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.

8. *Rare Diseases*

    a. Research utilizing innovative translational science approaches including development and validation of novel biomarkers for use in rare disease patient diagnosis, early phase dose-finding studies, evidence supporting efficacy or safety, and surrogate endpoints to advance rare disease drug development.

9. *Tobacco*
    a. Impact of tobacco product use on biomarkers of potential harm, with a focus on products other than conventional cigarettes, including deemed products.
    b. Identifying biomarkers of potential harm to assess short- and long-term health effects of tobacco products, with a focus on products other than conventional cigarettes, including deemed products (e.g., ENDS, heated tobacco products).

10. *Women's Health*

    a. Identify, develop, evaluate, and qualify biomarkers that can better measure and predict the safety and efficacy of FDA- regulated products in women in non- or preclinical studies and during clinical trials.

    b. Identify, develop, and evaluate biomarkers for the identification of sex differences in the performance of medical products

E. Clinical Outcome Assessment (COA)

Examples: Patient-reported outcomes; Clinician reported outcomes; Performance outcomes, Patient focused drug development.

1. *Devices*

    a. Develop methods for predicting, evaluating, and monitoring clinical performance of devices and materials.
    b. Modify or adapt existing Clinical Outcome Assessment instruments for a new subpopulation (e.g. pediatric subpopulations), regulatory use, intended use or context of use and collect evidence to support the modification or adaptation.

2. *Drugs*
    a. While registrational trials of analgesics have focused on changes in pain intensity as the primary endpoint, patient function is also critical to understand the benefit of an analgesic. Validated measures of function used in clinical trials are largely patient-reported. Submit proposals for further development of both objective and subjective measures of function which are critical to understand the benefits of analgesic therapies.

3. *Oncology patient-focused drug development*
    a. Investigate the sensitivity and measurement characteristics of existing patient-reported physical function measures in patients with rare and ultra-rare cancers.
    b. Investigate open label bias: evaluate the impact of patient's knowledge of their treatment on patient-reported outcomes in cancer clinical trials.
    c. Evaluate differences in measurement characteristics between core patient-reported outcomes collecting in US vs. ex-US oncology patient populations
    d. Study existing methods and develop novel methods to measure patient-reported symptomatic ocular toxicity in patients receiving anti-cancer therapy
4. *Rare Cancers, Oncology*

    a. Studies to develop and characterize symptom function measures for rare cancers or rare tumors to complement information obtained from traditional clinical trial endpoints used in regulatory submissions.
5. *Immuno-Oncology*

    a. Support research to improve understanding of the side effects of immune checkpoint inhibitors.

6. *Pediatric Oncology*

a. Investigations to solicit children's self-report of treatment related adverse events to accommodate the child's voice in assessing patient tolerability of new drugs.

7. *Racial and Ethnic Minority Health*

   a. Foster and assess the development of culturally and linguistically appropriate clinical outcome assessments and biomarkers to better understand health inequities and develop improved medical products;
   b. Improve upon patient science tools for medical devices through targeted incorporation of diverse patient perspectives and integration of data from diverse patients.
   c. Conduct studies among racial and ethnic minority communities and underserved populations (e.g., rural, elderly, pediatric populations and their parents/ caregivers) that investigate patient preferences in benefit-risk assessments to advance understanding and aid regulatory decisions.

8. *Women's Health*

   a. Assess the impact of lifestyle factors, including but not limited to, diet, exercise, and stress on health conditions that uniquely or disproportionately impact women
   b. Develop and validate new patient-reported outcome measures that capture the unique experiences and challenges faced by women in relation to their health

F. **Complex and Novel Clinical Trial Design**:

Examples: Complex, Adaptive, Bayesian, and/or other novel clinical trial designs. Methods may include design elements and/or analysis approaches that generally require computer simulations to determine the statistical properties of a clinical trial (e.g., power, Type I error). Methods for considering different endpoints, approaches for utilizing and validating artificial intelligence, machine learning, and natural language processing

1. *Devices*

   a. Evaluate the effectiveness of interventions designed to enroll diverse populations in device clinical trials such as digital health technologies, decentralized clinical trials, blood microsampling, patient/community/language navigators;
   b. 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 (e.g., rural, pediatric, elderly, or tribal populations) participating in device clinical trials;

c. Develop framework for assessing clinical site readiness to achieve adequate enrollment of participants from historically under-represented racial and/or ethnic minority populations in medical device clinical trials.
d. Medical device studies incorporating use of telemedicine and/or decentralized approaches (e.g., collecting laboratory and/or imaging data from local facilities) for patient assessments to facilitate clinical trial enrollment.
e. Encourage innovative device clinical trial designs and data analysis approaches to address female/women-specific or sex- and gender-specific issues.

2. *Drugs*
   a. Explore the role of digital health technologies (e.g., actigraphy, photography and other sensors) in the evaluation of new medical products, including validation methods and endpoint development.
      i. Compare digital measurements to traditional measurements in clinical trials.
      ii. Develop and evaluate novel endpoints using DHTs.
      iii. Compare metrics to evaluate continuous measurements (e.g., maximum activity and stamina).
      iv. Other proposals to support the innovative use of DHTs in drug development.
   b. Data informing the relative risks and benefits of long-term opioid therapy compared to non-opioid therapy are critical to the management of patients with chronic pain. Additional data is needed to assess if active controls (in addition to placebo) are beneficial in opioids, as well as study designs with multimodal treatment of pain and the feasibility of such studies

3. *Oncology trial designs, endpoints and statistical methodologies*
   a. 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.
   b. Develop statistical methods to assess bias and misclassification when RWD is used in estimating treatment effect.
   c. Multi-disciplinary research that includes expert clinical and statistical input addressing how external control data can be used as supportive data to isolate the treatment effect of experimental combination therapies.

d. Develop innovative clinical trial designs to find the optimal dose for oncology therapeutics.
e. Research relating to the design and analysis of pragmatic trials, for example using cluster randomization techniques
f. Develop statistical methods for ruling out detrimental treatment effects on overall survival in clinical trials of indolent cancers.

4. *Pediatric Oncology*
   a. Evaluate (in collaboration with statistical experts) novel study designs for small populations including Bayesian approached to borrowing from adult data and relaxed type 1 error considerations to facilitate randomized trials wherever possible.
   b. 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 strong scientific rationale that addresses the current data suggesting lack of activity of single agent ICIs in pediatric tumors.

5. *Immuno-Oncology*
   a. Develop clinical trial endpoints that account for atypical response patterns and more fully characterize the clinical benefit of ICI and other cancer immunotherapies.
   b. Develop clinical trial designs that can help capture atypical response to ICI and other cancer immunotherapies and can facilitate therapeutic development in immune-therapy resistant settings.
   c. Research that can improve prospective planning of clinical trials and analysis in the presence of non-proportional hazards for time-to-event endpoints

6. *Neo-antigen-based therapies, Oncology*
   a. Develop innovative trial designs (e.g., master protocols) 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.
   b. Develop innovative clinical trial designs to establish safety and efficacy in cell and gene therapies in randomized clinical studies where feasible.

7. *Health equity and special populations, Oncology*
   a. Evaluate the effectiveness of interventions designed to enroll diverse populations in oncology clinical trials such as digital health

technologies, decentralized clinical trials, patient/community/language navigators, not otherwise reported.

b. 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.
c. Develop framework for assessing clinical site readiness to achieve adequate enrollment of participants from historically under-represented racial/ethnic subgroups in therapeutic oncology clinical trials.
d. Conduct qualitative research to understand barriers to including underrepresented groups in oncology clinical trials (e.g., access to clinical trial sites, patient and/or physician preference, and/or other structural, operational, or trial-specific barriers), not previously reported
e. Identify best practices for enrolling underrepresented subgroups in oncology clinical trials, including patient-, physician-, and community-focused approaches, not previously reported.
f. Identify best practices for data collection to characterize the experience of persons who are members of sexual and gender minority groups, in cancer clinical trials
g. Identify best practices to conduct multi-regional cancer clinical trials in regions of the world not traditionally represented in global cancer trials (e.g., Africa, Central America, South America).

8. *Rare Cancers, Oncology*
    a. Studies in rare cancers 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.

9. *Racial and Ethnic Minority Health*
    a. 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, 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;
    b. Improve clinical study design and conduct to better identify and evaluate possible differences related to racial and ethnic minority populations, and/or pediatric populations, related to FDA-regulated products.
    c. 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 minority communities and underserved populations;

d. Identify methods to improve data collection in clinical trials for racial and ethnic minority communities, as well as rural and underserved populations (rural, elderly), including the use of remote clinical trials and evidence generation tools to support remote clinical trials.

10. *Rare Diseases*
    a. 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;
    b. In particular for orphan products, assess effectiveness of programs and incentives to address unmet medical needs in the rare disease population.

11. *Tobacco*
    a. Incorporate machine learning into clinical studies identifying unique biomarkers of potential harm associated with specific tobacco products or product types.

12. *Women's Health*
    a. Improve clinical study design and conduct to examine diseases and conditions primarily affecting women across the lifespan, including during pregnancy, lactation, and pre- and post- menopause.
        i. Develop analytical methods for interpreting and using data on sex differences from trials and studies with small sample sizes.
        ii. Identify and evaluate best practices for the recruitment and retention of women in clinical trials (e.g., new strategies, approaches).
        iii. Identify appropriate endpoints and outcome measures, including patient reported outcome measures, for diseases or medical products that may affect women differently from men (e.g., certain types of cardiovascular disease present differently in men than in women).

G. **Predictive Toxicology**

Examples (include traditional and novel methods): Biocompatibility; MPS; Identify potential toxicity; Determine acceptable and safe dose levels; Comparative and rare toxicity; Identify human relevance of toxicity findings

1. *Cross-cutting*

a. 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.

b. 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 sub-populations (e.g., pediatric populations).

c. 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.

d. Develop toxicologic and pharmacologic tools to assess and characterize molecular targets, host genetic and inflammatory factors that may be associated with rare and unexpected adverse events ("off-target" drug effects).

e. Develop and use MPS, CIVM, and modeling approaches to predict toxicity.

2. *Drugs*

a. Systematic Review of Pre-Clinical Studies on Anesthetic Induced Neurotoxicity – Published studies in pregnant animals and young animals have shown that use of general anesthetics and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the brain as well as behavioral changes. Given the difficulties associated with conducting controlled studies with anesthetics in children, animal models are important to characterize how early life anesthetic exposure affects brain development. To better understand the scope and magnitude of this problem, better inform the public about this risk, and develop strategies to mitigate this risk, we are developing approaches for creating living systematic reviews of pre-clinical studies of anesthetic induced neurotoxicity.

3. *Health equity and special populations, Oncology*
   a. Applied research to improve the understanding of the pathophysiologic process of cancer in members of underrepresented minority groups that can have a practical impact on oncology drug development
   b. Applied research addressing clinical pharmacology assessment in underrepresented populations (e.g., pharmacokinetic,

pharmacodynamic and/or pharmacogenetic analyses) that can have a practical impact on oncology drug development.

4. *Tobacco*

a. Evaluate critical toxicity mechanisms and modes of action for key constituents of ENDS, including Harmful and Potentially Harmful Constituents (HPHCs) that drive cancer and non-cancer toxicological risk.

b. Develop computational toxicological models to predict toxicity from a mixture of ingredients or HPHCs in aerosols from ENDS and/or their constituents.

5. Women's Health

i. Investigate the differences in pharmacokinetics and pharmacodynamics between sexes to determine how drug absorption, distribution, metabolism, and elimination may impact toxicity predictions and optimal dosing

ii. Identify specific biomarkers and genetic factors that contribute to sex-based variations in drug metabolism and response, and evaluate their role in predicting potential toxic effects.

iii. Investigate the impact of hormonal fluctuations, such as those occurring during the menstrual cycle and menopause, on drug metabolism and toxicity, and integrate this knowledge into predictive models.

H. Methods for Assessing Behavioral, Economic, or Human Factors

Examples: Human factors or usability engineering processes; Qualitative and quantitative social and behavioral data analysis; Usability and optimization of interactions between the FDA regulated product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc.

1. *Devices*

a. Develop methods to evaluate the magnitude of impact of morbidity and mortality on pediatric populations (especially younger subpopulations), and on resource utilization (e.g. economic impact) within the healthcare system due to the relative lack of devices designed, evaluated, and labelled for pediatric populations and the associated need for "off-label" or physician-directed care.

b. Develop and evaluate options to improve financing and reimbursement, and de-risk business investment, to increase pediatric medical device development and innovation, thereby mitigating the long-standing public health inequity impacting pediatric populations and pediatric healthcare.
c. Use human factors engineering principles in device and combination product design to improve usability of devices for all populations (especially underrepresented, pediatric, elderly, rural, or tribal populations).
d. Develop methods to identify and mitigate usability challenges related to sex- and gender-based differences. Support innovation in sex- and gender-conscious engineering design and development of medical devices.

2. *Drugs*
   a. Human Factors considerations for biosimilars and generics:
      i. Evaluate whether the comparative use human factors study methodology described in the draft Guidance, Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry, is an acceptable approach to assess whether differences in the user interfaces between a proposed interchangeable product and a reference product will lead to a difference in safe and effective use when the interchangeable product is substituted for the reference product.
      ii. Develop an acceptable methodology, or acceptable methodologies, to assess whether differences in the user interfaces between a proposed biosimilar interchangeable product and a reference product will lead to a difference in safe and effective use when the interchangeable product is substituted for the reference product.
      iii. Produce data that provides scientific clarity about (1) what user interface differences may affect the safe and effective use of the biosimilar interchangeable product as compared to the reference product when the biosimilar interchangeable product is substituted for the reference product, or (2) when the differences in the user interfaces between a proposed interchangeable product and a reference product should be further evaluated to determine if they affect safe and effective use of the biosimilar interchangeable product as compared to the reference product when the interchangeable product is substituted for the reference product.
      iv. Evaluate how existing data sources can be used to evaluate differences in the user interface between a proposed biosimilar interchangeable product and its Reference Product, including in

circumstances where the proposed interchangeable is already approved and marketed as a biosimilar.

b. Proprietary Name Evaluation: Research root causes and contributing factors for name confusion medication errors involving proprietary names when used in healthIT software systems across various aspects of the medication use process (e.g., computerized physician order entry, automatic dispensing cabinets, smart infusion pumps, inventory and procurement systems, pharmacy admixture software, electronic health records, etc). The goal is for FDA to apply such knowledge towards the systematic evaluation of the acceptability of proposed proprietary names.

3. Tobacco

a. Evaluate human factors principles in device access restrictions on tobacco products (especially ENDS).
b. Explore the potential impact of device access restrictions on tobacco use behavior among tobacco users and non-users.

I. Approaches to Incorporate Patient and Consumer Input

Examples: Patient and consumer preferences and perspectives; Empowering patients and consumers to make better-informed decisions

1. *Cross-cutting*
   a. 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;
   b. Develop and validate methods for collecting patient experience data;
   c. Correlate these patient experience data to product quality management maturity at the firm level;
   d. 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).

J. Methods to Assess Real-World Data (RWD) to serve as Real-World Evidence (RWE)

Examples: Generation of RWD from electronic health records (EHRs), claims and billing activities, product and disease registries, patient-generated health data including in home-use settings, and/or data gathered from other sources that can inform on health status, such as mobile devices; Analysis and assessment methods of RWD; RWE generation from RWD such as registries, observational data, electronic health records, claims data, diagnostic data,

patient-generated health data) are “fit-for-purpose” to serve as RWE(considerate of device development, innovation and labeling for pediatric populations):

1. *Cross-cutting*
    a. Leverage existing and future data to develop new tools and methodologies to harness big data and RWD (e.g., data derived from EHRs; medical claims and billing data; data from product and disease registries; patient-generated health data, including from in- home-use settings including diagnostics; and data gathered from other sources that can inform on health status, such as digital heath technologies (DHTs) like wearables or mobile applications) to support regulatory decision-making.
    b. Advance methodologies to generate clinical evidence from RWD sufficient to support regulatory use (considerate of device development, innovation and labeling for pediatric populations):
        i. Incorporate RWD sources in innovative clinical trial designs,
        ii. Demonstrate how clinical evidence generated from RWD could inform randomized controlled trials for regulatory use,
        iii. Develop and validate tools and models that assess the quality, interoperability, and utility of RWD to support regulatory decision making,
        iv. Develop and validate methods to predict and evaluate medical product performance using RWD,
        v. Using a collaborative approach, identify high-priority areas for development of RWD source methodology that meet stakeholder needs,
        vi. Evaluate methods of observational study design with a focus on identifying and/or addressing sources of (methodological) bias,
        vii. Explore methodological reasons for discordant findings among randomized and observational analyses addressing the same clinical topic involving FDA- regulated products,
        viii. Advance causal inference based on RWE;
    c. Leverage existing and future data to compare use of RWD and generation of RWE with more traditional approaches for data collection and evidence generation.
    d. Develop and demonstrate tools for assessing uncertainty around data elements and drives for RWE study findings.

e. Methods to evaluate the capture, transmission, aggregation, analysis, and use of DHTs to support medical product development and assessment.

f. Explore the use of data from DHTs to inform public health decision-making.

g. Support the capture, harmonization, transmission, aggregation, analysis, and use of high-quality, interoperable diagnostic data from real-world settings to evaluate in vitro diagnostic devices and other medical product performance during clinical trial development and premarket review

h. Explore how RWD obtained from in vitro diagnostic devices can be used to inform regulatory decision making across the total product lifecycle (including pre- and post-market)

i. Clarify and evaluate the current challenges and opportunities, considerate of the above noted options, in the collection and use of RWD to generate RWE for the purposes of pediatric medical device development and innovation.

j. Leverage existing registry networks for devices used in both males/men and females/women to evaluate for sex- and gender-specific differences.

2. *Biologics*
   a. 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.

3. *Biosimilars*
   a. Investigate and evaluate the data and information (including RWE) needed to meet the safety standards for determining interchangeability under section 351(k)(4) of the PHS Act.

4. *Oncology real world data and real-world evidence*
   a. Developing approaches to evaluate, integrate, and facilitate the use of oncology RWD, e.g., electronic health records, administrative health claims, drug or disease registries, patient reported or generated health data to generate high quality RWE is an active area of regulatory science as noted in the 21st Century Cures Act. Methodologically rigorous research which expands upon the need to evaluate innovative study approaches such as pragmatic clinical trials or other prospective

designs including development of RWD resources through high quality registry studies to accelerate clinical development of new drugs in oncology 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.

b. Evaluation of innovative applications of RWD to clinical drug development, including epidemiologic and statistical approaches, specifically through scientific methods research to enhance evaluation and assessment of RWD through evaluation of bias, confounding, or other potential threats to study validity. Examples include investigations to explore appropriate uses of externally controlled designs in clinical drug development.

c. Explore and define RWD quality through a research study or framework development to consider factors including data reliability and relevance including (but not limited to) factors such as collection missingness, specificity, sensitivity, data validation, data provenance, data harmonization, interoperability, data linkage and the potential capability to make accurate inferences from the available data or improve standardization efforts in the source data towards learning healthcare systems

d. Methods-focused research using artificial intelligence to analyze, assess and interpret the scientific literature and RWD to enhance understanding for potential uses in regulatory science

e. Develop, define and test real-word oncology endpoints in RWD that could be used to generate RWE to complement traditional clinical trial data submitted to FDA, particularly the development of measures of real-world response and validation of such endpoints.

5. *Oncology Safety*
   a. Develop improved and standardized approaches to collect and analyze cardiotoxicity data in the context of clinical trials to support new indications

6. *Pediatric Oncology*
   a. Investigations to explore opportunities to develop appropriate external control arms using RWE or clinical trial data to aid in clinical development of new drugs for pediatric cancer.

7. *Precision Oncology*
    a. Develop methodologies to assess RWD as supportive evidence generation (clinical trial design; use of real-world data for liquid biopsy diagnostics that are assessing multiple cancer types simultaneously for early detection indications (multicancer early detection [MCED]), along with the data from prospective clinical studies that are needed as clinical validation for MCED assays.
    b. Studies, including registries, to understand the epidemiology and rates of biomarker testing in patients with cancer, such as studying the prevalence of rare genomic subsets of clinical interest in patients with cancer.

8. *Immuno-Oncology*
    a. Analyze RWD to understand the utilization and impact of complementary in vitro diagnostics in cancer immunotherapy.

9. *Health equity and special populations, Oncology*
    a. 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;
    b. Study RWD to understand patterns of care and clinical outcomes in sexual and gender minorities with cancer.

10. *Rare Cancers, Oncology*
    a. Studies, including registries, to understand the natural history of rare cancers to provide clinical and scientific context to inform the design and interpretation of clinical trials
    b. Investigations to explore opportunities to develop appropriate external control arms using real world evidence or clinical trial data to support the clinical development of new drugs for rare cancers

11. *Rare Diseases*
    a. Explore mechanisms to support and expedite development of approved drugs for non-cancer rare disease indications (i.e., repurposing) such as analyzing RWD (e.g. registries) to inform screening and evaluation of drugs in rare populations.

12. *Tobacco*

External validity of data related to Modified Risk Tobacco Product claims:

a. Assess and evaluate the behavioral effects of real world, multiple exposures to modified risk tobacco product claims (i.e., longitudinal effects).

b. Develop a methodology to model or predict future real-world outcomes using data collected in constrained scientific studies related to exposure or intentions about modified risk tobacco products. Evaluate how best to take cross-sectional data and extrapolate it to long term outcomes.

13. Women's Health

a. Evaluate methodologies for the identification of clinically relevant sex differences, using a variety of RWD sources

b. Conduct studies using RWD to evaluate the toxicity or the safety, effectiveness, and health effects of FDA-regulated products used by women, including the examination of sex differences

c. Develop efficient data mining and analysis techniques that can be used on RWD sets that can specifically identify women's health issues on a larger scale.

K. Methods to Assess Data Source Interoperability

Examples: Development of methods, tools, framework and data sources for safe, secure, effective, portable, and interoperable exchange of information among one or more FDA regulated products, technologies, or systems.

1. *Cross-cutting:*

   a. Develop standards for data quality and data sources that increase the quality, interoperability, and utility of RWD;
   b. Design and optimize data infrastructure to facilitate information exchange and data extraction.
   c. Develop, improve, and/or harmonize data standards applied for use in regulatory submissions including information supplied to FDA through the electronic Common Technical Document (eCTD) and/or other submission mechanisms used by FDA.
   d. Develop methods to incorporate data from DHTs not in EHRs into patient care beyond clinical trials.

II. Strengthen post-market surveillance and labeling of regulated products

The following focus areas of regulatory science are identified to accomplish Charge II, *strengthen post-market surveillance and labeling of FDA-regulated products*:

A. Methodologies to Assess Real-World Data (RWD) to serve as Real-World Evidence (RWE)

Examples: Generating evidence regarding safety and effectiveness using RWD for FDA regulated products; Supporting FDA's regulatory decisions of

effectiveness using RWE informed by RWD; Development and application of methods for RWE generating using RWD for post-market surveillance of FDA regulated products.

1. *Cross-cutting*
    a. Refine methods for analysis of post-market data, including data mining of spontaneous reports and analysis of data accessible from large healthcare databases and electronic health records.
    b. Leverage real-world evidence and employ evidence synthesis and linkage across multiple domains to support regulatory decision-making;
    c. 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;
    d. Support the capture, harmonization, transmission, aggregation, analysis, and use of high-quality, interoperable diagnostic data from real-world settings to aid in pre-market submissions, post-market review and/or surveillance of safety and performance of in vitro diagnostic devices and other medical products;
    e. Demonstrate how RWD obtained from in vitro diagnostic devices during post-market surveillance and data collection can be used to inform regulatory and public health decision-making.

2. *Devices*
    a. Develop approaches for collecting data on mortality and reuse among patients exposed to capital and reusable devices and how to integrate within EHRs, administrative claims, or other RWD.
    b. Develop methods to better encode physiologic and social determinants of health data elements that may pertain to safety and efficacy of diagnostics and therapeutics targeting women.

3. *Drugs*
    a. Studies to evaluate the safety of approved drug products:
        i. 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.
        ii. Identify RWD or other data sources and methods to determine when safe use conditions that are required in a REMS have been integrated into medical practice or the healthcare system
        iii. Develop predictors that can be used to determine when safe use conditions that are required in a REMS are likely to be integrated into medical practice or the healthcare system

iv. Evaluate how registries contributed to drug and/or REMS approval; and how registries can monitor certain safe use conditions that are required in a REMS. The scope would include identifying and describing best practices for implementing registries for drugs that are subject of a REMS.

b. Advance medication error pharmacovigilance:

i. Develop methods and determine the scope of medication errors associated with nonprescription monograph products. The scope would include incidence, types of errors (e.g., incorrect dose, wrong drug selected, wrong route of administration), contributing factors for the errors (e.g., look alike carton labeling, confusing directions for use or packaging, dosing device difficult to use), and adverse events or outcomes.

ii. Research how differences in dosage forms (e.g., gelcaps, liquids, effervescent tablets, gummies, sublingual films, lollipops) between orally administered nonprescription monograph products contribute to unintentional pediatric exposures or overdoses and determine if certain dosage forms have a higher incidence of unintentional pediatric exposure than others.

4. *Oncology safety*
   a. Develop approaches for collecting medical product safety data from RWD sources to expand understanding of the safety profile of approved oncology products in clinical practice;
   b. Conduct analyses using RWD sources in cancer patients with a history of or active COVID-19 infection to evaluate increased severity of known known drug adverse reactions or new toxicities, longitudinal sequelae, and residual toxicity;
   c. Analyze RWD to help understand which patients are most likely to experience cardiotoxicity (or other types of severe toxicity) during cancer treatment.

5. *Women's Health*
   a. Evaluate and validate U.S. and international RWD sources for use in the identification of the potential adverse effects and sex differences on the safety and effectiveness of FDA-regulated products used by women.
   b. Evaluate methodologies for the identification of clinically relevant sex and gender differences, using a variety of RWD sources

c. Conduct studies, using RWD sources to evaluate the safety and effectiveness, of FDA-regulated products used by women, including the examination of sex and gender differences

B. Using and Validating Artificial Intelligence Approaches

Examples: Machine learning; Deep learning; Natural language processing; Large Language Models, Generative AI

1. *Cross-cutting*
   a. Develop and validate a tool that uses natural language processing, large language models, machine learning or artificial intelligence to semi-automate review of medical charts to improve, expedite, and lower chart review costs.
   b. Large language models (LLM) to develop and improve the efficiency of signal detection/data collection methods and operations such as computable phenotype generation in support of future post-market active surveillance systems for medical products.
   c. Develop and evaluate risk-based methods for the validation and implementation of artificial intelligence approaches in the development, manufacturing, and quality system activities for medical products
   d. Develop tools to understand and assess LLM and their application in healthcare

2. *Devices*
   a. Develop and validate methods to assess algorithm performance, including techniques to manage bias for artificial intelligence/machine learning-enabled medical devices
   b. Develop tools or methodologies to evaluate the performance of large language models/generative AI as they are applied to devices including methodologies that would enable robust post-market monitoring to ensure continued high-quality performance of LLM-enabled devices, including identifying and preventing data drift, and ensuring ongoing model accuracy

3. *Drugs*
   a. Studies to increase the safety of post-approval drug use: 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;
   b. Studies to evaluate the safety of approved drug products:

i. 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. Evaluate whether use of controls charts prospectively is feasible to assess for adherence to REMS requirements in real time.

ii. Explore and apply the use of NLP models and advanced algorithmic and unsupervised machine learning (ML) techniques to analyze medication error-related reports, and data submitted to FDA, and electronic health records, including techniques to identify and assess medication error safety signals, human factors, contributing factors, data quality, and other variables.

4. *Women's Health*

a. 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 post-market safety and utilization of FDA-regulated products to specifically identify sex and gender differences or women's health issues.

b. 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.

C. Novel Clinical Trial Design, Statistical and Epidemiologic Methods

Examples: Novel and advanced methods to improve post-marketing surveillance of FDA regulated products

1. *Cross-cutting*

a. Develop methods to harness clinical evidence and enhance evidence synthesis to leverage RWD from multiple domains;

b. Develop statistical methods for assisting compliance inspection.

c. Advance methods for endpoint adjudication/validation to incorporate predictive RWD analysis and/or probability that determination impacts study findings

2. *Oncology Safety*

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

b. Conduct basic, translational or clinical studies that investigate the underlying causes of cardiac toxicities associated with approved oncology agents.
c. Develop novel approaches to utilize AI/ML to mine different data sources (e.g., EHRs, claims) for new safety signal identification and/or further characterization of the safety of oncology therapeutics.
d. Develop models and/or new translational study designs to better understand the mechanisms of toxicity underlying causes of recent safety alerts issued by FDA oncology.

D. Automated Reporting Tools for Adverse Events and Active Surveillance

Examples: Develop and/or enhance passive and active surveillance systems, frameworks, and/or methods to monitor post-market safety, effectiveness, quality, and availability of FDA regulated products

1. *Cross-cutting*

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

a. Advance the study of quality management maturity, and organizational excellence; including quality metrics and quality culture, supply chain oversight and insight, inventory management, application of quality 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;

b. Advance statistical methodology, including signal detection, 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 quality surveillance programs;

c. Develop tools that can combine diverse and incomplete data sets to provide a more thorough understanding and visualization of supply chains and the volume/market presence of products

d. Develop and evaluate methods for prioritizing quality defect report assessment, surveillance sampling, and surveillance inspection prioritization;

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

f. Advance methodologies to conduct modular active surveillance statistical analysis while accounting for patient privacy and maintaining line-level data with data holder.

2. *Biologics*

   a. *Compare safety alerting patterns generated using data mining methods between electronic health record databases and VAERS databases in terms of traditional performance metrics, signal characteristics, and time to detection.*

3. *Drugs*

   a. *Improve scientific approaches to evaluate generic drugs:* post market evaluation of generics drug to develop surveillance and monitoring methods for generic drug substitutions and characterize patient perceptions of generic drug quality and effectiveness.
   b. *Studies to increase the safety of post-approval drug use:* Develop innovative methods to create, facilitate and encourage research in the area of safe medication use that seeks to reduce preventable harm from drugs;
      i. 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:

         a) 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;

         b) 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;

c) Target populations may be broad (e.g., when addressing a common high-burden disease) or may be narrow, focusing on an unmet medical need in a vulnerable population (e.g., very young or elderly, minorities, women, veterans, economically disadvantaged groups, stigmatized populations, or those with a disability.

c. *Improve scientific approaches for conducting postmarket surveillance of drugs:*
   i. Compare safety alerting patterns generated using data mining methods between electronic health record databases and the FAERS database in terms of traditional performance metrics, signal characteristics, and time to detection.
   ii. Use data analytics, text analytics, and AI approaches to develop signal detection tools to detect quality problems for drug products and their manufacturing sites.

4. *Oncology Safety: Oncology Safety*
   a. Develop tools and/or algorithms to identify adverse reactions such as cytokine release syndrome, or other immune-related adverse events to eliminate the need for manual adjudication

E. **Methods to Improve Communication About Risk to Patients and Consumers**
Examples: REMS, safety recalls for medical products, food safety recalls, and support patient decision-making (e.g., patient-specific labeling, patient decision aids); Patient and consumer input; Qualitative and quantitative social and behavioral data analysis for post-market

1. Devices

a. Promote user-centered transparency of digital health medical devices (e.g., artificial intelligence/machine learning-enabled devices, virtual reality devices)

b. Identify and evaluate best practices for user-centered recall communications, including but not limited to the level of detail in communications for patients, formatting and delivery strategies, and the timing and updating of communications as information becomes available

2. *Drugs*

   a. Studies to evaluate the safety of approved drug products:

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

      ii. Improve the quality and effectiveness of Risk Evaluation and Mitigation Strategy (REMS) programs in communicating risk to patients.

      iii. Identify practice models and characteristics of interventions that promote integration of informed benefit-risk decision making into clinical practice.

      iv. How to define and measure the effectiveness of informed benefit-risk counseling and decision-making for products that are subject to a REMS.

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

3. *Tobacco*

   a. Evaluate how risk information in modified risk tobacco product claims influence different audiences, especially adults vs. youth, and what factors of claims are attractive to each audience.
   b. Assess the aspects or factors of modified risk tobacco product claims that might lead to unintended consequences of non-users of tobacco initiating tobacco use or experimenting with modified risk tobacco products.

3. *Women's Health*

   a. Identify how factors such as sex, gender, age, literacy level, and native language can affect a woman's understanding of FDA product information and its influence on her subsequent health-related decisions
   b. Evaluate the reach and impact of FDA communications about FDA-regulated products used by women, including but not limited to identifying and evaluating methods for communicating:
      i. FDA information to special populations of women, including elderly women, women with disabilities, caregivers, pregnant and lactating women, and women with limited English proficiency
      ii. Specific information about sex and gender differences
      iii. Risks of certain medical product exposures, food consumption (e.g., seafood), and the use of tobacco products during pregnancy and lactation

iv. Information about drug exposure during breast-feeding

c. Explore methods for using social media to identify gaps in knowledge, misinformation, or sentiments about specific women's health issues and related FDA regulated products.

F. Approach to Expand Data Capacity, and Increase Data Quality and Use

Examples: Data expansion, modernization, and enhancement to improve post-market safety surveillance and labelling

1. *Cross-Cutting*

   a. 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, evaluation of sex differences, different genders, and geographical location.

2. *Drugs*

   a. Data informing the relative risks and benefits of long-term opioid therapy compared to non-opioid therapy are critical to the management of patients with chronic pain. Additional data is needed to assess if active controls (in addition to placebo) are beneficial in opioids, as well as study designs with multimodal treatment of pain and the feasibility of such studies.

3. *Racial and Ethnic Minority Health*

   a. Develop and analyze large scale clinical data sets to determine comparability of non- US data to the US population and refine methods for analysis of large healthcare databases and electronic health records to advance understanding of treatment outcomes by racial and ethnic minority populations.

G. Efforts to Harmonize Existing and Emerging Data Standards

Examples: Methods and frameworks to improve the quality, accessibility, shareability of data standards applied for, but not limited to, post-market surveillance

1. *Cross-cutting*
   a. Improve existing or develop new approaches to enhance agility, quality, and consistency of regulatory submission data, and to

harmonize standards for data synthesized across multiple sources, including data captured from in vitro diagnostic devices

b. Harmonize healthcare and clinical research data standards including their value sets primarily using the data standards as defined by the Office of the National Coordinator for patient care (e.g., SNOMED, LOINC, RxNorm); maintain the mappings provenance across standards

c. Enhance existing implementation guides for data standards

III. Invigorate public health preparedness and response of the FDA, patients, and consumers

The following focus areas of regulatory science are identified to accomplish Charge III, *invigorate public health preparedness and response of the FDA, patients, and consumers*:

A. Reinforce Medical Countermeasures Initiative (MCMi) to Increase Preparedness and Response for Emerging Public Health Threats

Examples: Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency. 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.

1. Develop and fully characterize tools to support MCM development under the Animal Rule, Accelerated Approval, or Emergency Use Authorization (EUA):

a. Advance the capability to conduct natural history studies necessary to support MCM development under the Animal Rule, including novel approaches toward replacement of non-human primate (NHP) studies

b. 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);

c. Develop, qualify, and/or facilitate innovative analytical technology 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;

d. 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 models and humans;

e. 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;

f. 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);

2. *Enhance the agility, quality, and utility of diagnostics and diagnostic data:*

   a. Support enhanced regulatory science tools and data for novel diagnostics and diagnostic approaches, including next-generation sequencing, real-world evidence (RWE), etc.
   b. Support regulatory science approaches toward diagnostics in the context of advanced manufacturing
   c. Support enhanced data agility of data collection using medical devices and through the use of enhanced data collection methods associated with medical products that could be harnessed during public health emergencies

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

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

   i. Develop and refine tools and methodologies to collect, monitor, track, and analyze real-world data and real-world evidence to support regulatory and public health decision making,

   ii. Develop capabilities to inform or support multisite/multi-center clinical studies including pre-positioned protocols, rapid and flexible clinical trial designs, novel statistical methods for analysis of clinical data, and clinical trial networks;

b. Develop and validate reference materials and datasets to facilitate the development of medical products related to relevant CBRN threat agents and emerging infectious diseases;

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

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

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

f. Develop technologies and methods to monitor and predict disruptions in medical device/medical product supply chain security due to technological or CBRN threats;

g. Explore novel approaches, technologies, platforms, and frameworks to increase the ability of suppliers' flexibility and ability to respond to supply disruptions, and streamline supply chains.

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

a. 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.);

b. Develop technologies and methods to accelerate collection of MCM-relevant clinical safety and efficacy endpoints;

c. Develop methods using digital design and manufacturing data to increase efficiency of review;

d. Develop technologies to support the adoption of advanced manufacturing technologies for MCMs

e. Evaluate methods for facilitating and incentivizing the production and development of MCMs or MCM supply chain within the U.S

5. *Devices*
   a. Develop analytical models to assess the risk of device recalls and shortages on small and special populations, especially pediatric populations.

6. *Rare Diseases*
   a. Develop drugs for emerging or sporadic diseases- e.g. MERS, drug resistant outbreaks and for underserved populations e.g. neonates, pregnant and lactating women.

7. *Racial and Ethnic Minority Health*
   Evaluate strategies for the prevention, diagnosis, and treatment of COVID-19 for potential racial and ethnic minority population related health effects. Explore strategies to enhance medical product development for diseases and populations with limited or absent approved treatment options.

8. *Women's Health*
   a. Develop tools to identify public health threats, prevent them from becoming crises, and promote public health security, with a focus on women.
   b. Assess whether medical countermeasures—such as drugs, vaccines, and diagnostic tests—include women during development and include an evaluation of sex differences.

B. Antimicrobial Resistance

Examples: Combat antibacterial and antifungal drug resistance; Facilitate the development of new antibacterial and antifungal drugs to treat patients; methods used to evaluate and improve product labeling of antimicrobial drugs

1. *Drugs*

   a. 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 information please visit www.fda.gov/oidresearch
   b. Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antifungal and antibacterial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction
   c. 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;
   d. Evaluate strategies to enrich enrollment in clinical trials for new drugs such as the use of rapid diagnostic tests.
   Evaluate the utility and impact of current methods and innovate strategies to communicate FDA evaluations of safety and effectiveness

of approved antimicrobial drugs to healthcare providers with the goal of appropriate use of new antimicrobial drugs.

C. Patient and Consumer Engagement and Communication

Examples: Engage and empower patient and consumer involvement in public health preparedness

1. *Cross-cutting*

a. Apply social and behavioral science to empower patients and consumers, enhance FDA's understanding of its audiences and decision-making about regulated products.
b. 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
    i. Identify effective ways to communicate so that patients and consumers, including those with low literacy/health literacy/digital 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 means of changing messages 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;

    ii. Study the impact of different formats and amounts of numerical information in FDA communications for consumers, patients, health care providers, health educators and informal caregiver

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

c. Assess public understanding of regulatory and scientific terminology and the impact this language has on the public's ability to comprehend FDA communications, and identify explanatory strategies or alternatives. Examples of FDA terminology include, but are not limited to, the following: safe and effective, Over-The-Counter (OTC), monograph drugs, voluntary recall, and product correction.
d. Explore ways that FDA communications can best enhance audience comprehension, including to complement those communicated by industry and other organizations
    i. Develop tools for measuring the effectiveness of messages being communicated to the public, including those with low

literacy/health literacy and limited English proficiency, by FDA communications, industry advertisements and other communication materials (e.g. webpages, social media), and messages developed by other organizations.

e. Evaluate timing of release of recall or warning messages, how and when these messages can enhance impact, and how to communicate recall updates and the end of a recall or warning.
    i. 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.
    ii. Develop best practices for communicating about recalls, including the necessary elements and appropriate levels of detail, accounting for differences in literacy/health literacy levels and level of English proficiency

f. Identify and improve science-based approaches that enhance awareness, understanding, and informed decision-making by patients, consumers and health care professionals to promote health and reduce harms of FDA-regulated products (excepting foods, dietary supplements, cosmetics, and products regulated by Center for Tobacco Products).

2. *Drugs*

a. Studies to evaluate the safety of approved drug products to advance the science of medication error prevention and analysis

    ii. Determine the incidence, public health cost burden, extent of underreporting, and causes of medication errors in the United States related to drug product names, labeling, packaging, or product design.
    iii. Identify and evaluate data sources and methods for medication error pharmacovigilance, including signal detection and case assessment used by global industry, regulatory agencies, and other applicable sources.

3. *Racial and Ethnic Minority Health*

a. Informing and enhancing audience understanding among diverse populations

    i. Assess awareness of FDA communications among racial and ethnic minority populations, as well as barriers and facilitators to use of FDA's materials.

ii. 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, low digital literacy, limited English proficiency, and cultural and language differences.

iii. Conduct studies to determine methods to improve communication strategies and reach among racial and ethnic minority communities and underserved populations.

iv. Conduct studies to inform development of FDA communications to racial and ethnic minority communities and underserved populations.

D. Understand Substance Use and Minimize Misuse

Examples: Opioids, Substance use disorders, Addiction to tobacco products

1. *Devices*
   a. Develop methods to leverage RWD in support of evaluation of digital health technologies relating to OUD and SUD
   b. Engage academic and community medical centers, patients, and other stakeholders in the evidence development needed for digital health technologies for OUD and SUD

2. *Drugs*

   2.1 Opioids

   a. Perform research to understand the relationships between buprenorphine-containing medication for opioid use disorder (MOUD) dosing strategies (e.g., dosing for induction, titration/stabilization, maintenance) and patient outcomes, including but not limited to fatal and nonfatal opioid-involved overdose. Consider additional factors such as use of other medications (e.g., opioid analgesics, anticonvulsants, anxiolytics, and other psychiatric medications); patient factors (e.g., pain, polysubstance use); and systemic and environmental factors (e.g., urbanicity, settings of care, and the evolving illicit drug supply).
   b. Perform research to provide information on the amount (e.g., number of doses, total milligrams) and formulation (e.g., tablets, oral solution) of methadone dispensed from U.S. opioid treatment programs as take-home doses and how this has changed over time. Also collect information on the use of specific measures to prevent unintentional exposures in children (e.g., child-proof containers, patient education programs, use of locked storage boxes).

c. Characterize neurodevelopmental and mental health outcomes in preterm infants exposed to opioid analgesics, and sedative and anesthetic agents. Despite significant nonclinical data, including data from nonhuman primates, suggesting there are risks of neurotoxicity associated with administration of these agents in pediatric patients three years of age and younger, human data are lacking. The goal of this research would be to further inform these risks in the most vulnerable pediatric population.
d. Review the information in the published literature to inform neurodevelopmental outcomes in children with cancer, graduates of pediatric intensive care units, and children with congenital heart disease who undergo frequent diagnostic and therapeutic procedures and surgeries, and require treatment with opioid analgesics, and sedative and anesthetic agents. The goal of this research would be to further inform the risk of neurotoxicity in these vulnerable pediatric populations.
e. FDA has developed a system dynamics model of opioid crisis (FDA Opioid Systems Modeling Effort | FDA), aligned with recommendation 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 dynamics of the crisis, and b) assessing the potential impacts (intended and unintended) of possible policy actions to address the crisis. FDA now seeks to viably incorporate state or regional level data into our systems modeling effort to allow for testing potential variable effects and consequences of a national policy, as well as any potential disproportionate impacts on the regional level.

2.2 Substance use disorders:

a. Perform research to enhance FDA's understanding of, and the evidence supporting, the features, methods to increase uptake, impact on medication use systems, benefits, and harms of packaging, storage, delivery, and disposal solutions that can reduce nonmedical use, accidental exposure, and overdose of opioids and other drugs that pose a serious risk of abuse or overdose.
    i. Examples of features that can be explored in the research include (1) the methods and extent of retrievability of active ingredients, (2) safety messages, (3) fixed quantity, (4) individual child resistant protection of each unit or dose, or (5) user interface design.
    ii. Examples of methods to increase uptake that can be explored in the research include (1) order sets, (2) computerized physician

order entry (CPOE) software, including exploration of software cues, positioning of medications, or other, (3) patient education

iii. Examples of impact on medication use system that can be explored in the research include (1) cost or economic impact

b. Identify and evaluate appropriate endpoints for studies undertaken to assess packaging, storage, delivery, and disposal solutions designed to reduce nonmedical use, accidental exposure, and overdose involving opioids and other drugs that pose a serious risk of abuse or overdose. Endpoints may include (1) rate of accidental exposures, (2) use of disposal options to discard leftover medication, (3) medication adherence, (4) unauthorized access of medication, (5) amount of leftover medication, (6) unintended consequences, and others. Compare direct measures of the extent of patient disposal of opioids and other drugs that pose a serious risk of abuse or overdose:

i. Across various prescription medication disposal options (e.g., mail back envelopes or in-home disposal systems) provided to patients, or

ii. When there is provision of education alone, when there is provision of a prescription medication disposal option alone, or when there is education plus provision of a prescription medication disposal option.

c. Conduct behavioral, economic, human factors, or other studies to assess prescriber, pharmacist, and patient reasons, knowledge, attitudes, beliefs, and challenges regarding accessing and using packaging, storage, delivery, and disposal solutions for opioids and other drugs that pose a serious risk of abuse or overdose. Such studies should consider factors such as cost, design features, availability, usability, stigma, and perceptions of risk;

d. Conduct studies of adults prescribed prescription stimulants for attention-deficit/hyperactivity disorder (ADHD) or other conditions to evaluate the associated risks of illicit stimulant use, substance use disorders (including, but not limited to stimulant use disorders), and stimulant-associated adverse outcomes (e.g., stimulant-involved emergency department encounters, long-term safety outcomes, self-reported adverse events). Consider analyses stratified by stimulant type (amphetamine vs methylphenidate), with population and non-stimulant ADHD control groups, as well as a contextual comparator group of individuals dispensed opioid analgesics. Both prospective and retrospective study designs are of interest. Feasibility assessment, causal models (e.g., directed acyclic graphs), and instrument or algorithm validation studies may be necessary.

2. *Tobacco*

a. Understand the effects of tobacco product characteristics on addiction and abuse liability among populations or groups that bear disproportionate burden of tobacco risk and harm. Priorities for addiction studies include: 1.) correlation of ENDS and nicotine pouches, use behaviors with pharmacokinetic and pharmacodynamics effects of nicotine and other HPHCs delivered by ENDS and nicotine pouches; and 2.) the relationship between specific flavor categories in ENDS and nicotine pouches (including, but not limited to, tobacco, menthol, fruit, and sweet/dessert) and adult users' interest in cigarette smoking cessation, reduced cigarette use, switching to potentially less harmful tobacco products, quit attempts, or tobacco cessation success.

3. *Women's Health*
   a. Assess the prevalence and patterns of substance use (including tobacco, alcohol, prescription medications, and illicit drugs) among pregnant women, and investigate its association with maternal mortality

E. One Health Approaches

Examples: Opportunities to collaborate in the research, development, evaluation, testing, and scaling of innovative, practical, and cost-effective strategies to assist with regulatory decision that address health issues prioritized by FDA's Office of the Commissioner and the One Health Steering Committee

1. *Cross-cutting*

   a. Development of surveillance systems and networks integrating human, animal, and environmental detection and measures assisting with regulatory decisions intended to prevent and prepare for emerging health threats.
   b. Develop methods to assess the impact of contaminants on human, animal, and environmental health, including the distribution and fate of contaminants in natural ecosystems, and develop tools to better assess risk and to predict how sources for human and animal exposures may affect the safety of medical products and human and animal food .
   c. Develop and apply One Health methods and criteria for collecting antimicrobial use data across species in food and production systems to include:
      i. Assessing direct and indirect impact of the use of antimicrobial drugs on the microbiome of non-targeted species;
      ii. Implementing culture independent methods to detect and quantify bacterial pathogens and associated antimicrobial resistance genes in food and environmental samples;

iii. Establishing methods and interpretive criteria for *in vitro* susceptibility testing methods for pathogens to support prudent antimicrobial use.

d. Develop, implement, and identify educational and training opportunities in sciences and technologies advancing One Health. The primary focus is to enhance a transdisciplinary workforce knowledgeable about One Health and how to integrate One Health knowledge and skills in FDA's regulatory activities.
e. Research enhancing One Health communication approaches and interventions influencing public trust, countering misinformation and disinformation, and supporting health education and promotion through existing mass media, social media, or other communication channels.
f. Develop One Health methods, which will contribute to the establishment of policies and programs, focusing on computer models that integrate human, animal, and environmental safety data to predict health risks and corroborate pre- and post-market findings for FDA-regulated products with relevancy across species.
g. Research and develop measures that can be taken to improve mitigation of and response to the impacts of natural or man-made disasters on human and animal food and medical products, including supply chains.

F. Strengthen Global Product Safety Net

Examples: Build regulatory capacity through training, tools to strengthen surveillance systems in developing countries; Harness informatics to ensure the safety of FDA-regulated products, framework, or methods to support and collaborate with regulatory systems across the globe

1. *Cross-cutting*

a. 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;
b. Analyzing and utilizing global data to manage risks

i. 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 operation and surveillance;

ii. Develop predictive models that identify risks, including fraudulent products and product demand surges, across the supply chain regardless of the product or its origin;

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

iv. Adopt new approaches to better aggregate and analyze multiple sources of information to fully identify supply chain risks and emerging trends based on comprehensive assessments of existing information platforms. The developed approaches should include data mining of intelligence-related sources (event reporting, testing results, alerts, customer complaints, news reports, raw material prices, etc.) 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;

v. 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.

2. *Biologics*

a. Global vaccine production*:*

i. Facilitate global access to vaccines and other biological products by building capacity for the infrastructure for the development, delivery and post-market surveillance

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

iii. 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.

3. *Drugs*

a. Medical product shortages: 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

i. 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.
ii. 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.

G. **Emerging Technologies**

Examples: Projects anticipating the "next new thing" and future trends in science and technology for FDA's regulatory research areas

1. Devices:

a. Methods to operationalize economies of scale in the manufacturing of emerging medical devices for pediatric populations, especially younger subpopulations

Part I Appendix *(Additional background)*

1. *Antimicrobial drug development and 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 and antifungal drugs to treat patients and (2) advance the science of clinical trial design. More information on specific funding priorities can be found at: www.fda.gov/oidresearch.

2. *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 related to these around of interest maybe found here: https://www.fda.gov/about-fda/oncology-center-excellence/oce-scientific-collaborative)

3. *Neo-antigen-based therapies, Oncology*: 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. 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

4. *Health equity and special populations, Oncology:* OCE 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). 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. *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

6. *Oncology real world data: Additional background information relating to this area may be found at : https://www.fda.gov/about-fda/oncology-center-excellence/oncology-real-world-evidence-program*

7. *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

8. *Oncology trial designs, endpoints 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

9. *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
10. *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
11. *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
12. *Drugs related Biomarker and Clinical Outcome Assessments:* Additional background information relating to these areas of interests may be found at Biomarker Qualification Program | FDA; Clinical Outcome Assessment (COA) Qualification Program | FDA; https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program
13. *Manufacturing Readiness Levels as defined by Department of Defense:* Additional background information relating to these areas of interests may be found at: http://www.dodmrl.com/ and further explained at: https://www.nextflex.us/wp-content/uploads/NextFlex_PC3.0_MRL-TRL_Definitions.pdf)
14. *Generic Drugs:* Additional background information GDUFA science and research priority initiatives for FY 2024.
15. *Medical Countermeasures (MCMs):* FDA seeks to facilitate development of safe and effective MCMs through both intramural research and collaboration with external partners (e.g., academia, U.S. government agencies, non-governmental organizations, and industry). The FDA's MCM regulatory science mission 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, including current and completed projects, 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
16. 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
17. Food and Drug Administration Overdose Prevention Framework. This framework consists of four priorities to address the overdose public health emergency. Additional background information is available at

https://www.fda.gov/drugs/drug-safety-and-availability/food-and-drug-administration-overdose-prevention-framework

18. MDUFA V Draft Commitment letter: Additional background information is available at https://www.fda.gov/media/157074/download
19. CDRH 2022-2025 Strategic Priorities: More information on CDRH's advancing health equity strategic priority is available at https://www.fda.gov/media/155888/download
20. AI/ML-Based SaMD Action Plan: Available at https://www.fda.gov/media/145022/download
21. Advancing Digital Health Medical Devices for Opioid Use Disorder: Available at https://www.fda.gov/news-events/fda-voices/fdas-budget-advancing-goal-ending-opioid-crisis
22. Digital Health Regulatory Science Research Spotlight: Digital Health Center of Excellence | FDA
23. Industry 4.0 for pharmaceutical manufacturing: https://www.sciencedirect.com/science/article/pii/S0378517321003598
24. Animal Rule: 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
25. One Health Approaches: The development of One Health approaches enhances the collection of cross-cutting data gathering focusing on the integration of human and animal FDA-regulated products impacted by environmental factors (e.g., physical, social, economic, or others) of national and global importance. One Health is a conceptual framework addressing the interconnectedness of human, animal, and environmental health. It provides a lens with which to analyze a diverse array of public health problems that includes but is not limited to food and drug adulteration and contamination, malfunctions and adverse events with medical devices, antimicrobial resistance across species, emerging pandemics, food insecurity, harm caused by tobacco use across species, climate change, health equity, food and medical supply chain issues, environmental justice, and chronic, non-communicable diseases. One Health is mentioned in recently published global and Executive Branch strategic plans and proposed bills such as the 2022 National Biodefense Strategy, the One Health Security Act, and the Quadripartite One Health Joint Plan of Action.

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 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.

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 attachment

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 (SOW).

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

***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 has two (2) stages as follows:

Stage 1: Submission of a freestanding Concept Paper **and** freestanding Full Proposal in accordance with the preparation guidance in Section 2 of Part III – see Table 2 for detailed timelines. Freestanding Concept Papers shall describe the effort in sufficient detail to enable a high-level evaluation of the concept's technical merit and its potential contribution as well as program alignment with FDA priorities and mission. Evaluation of Concept Papers will be conducted by scientific experts leading the various FDA Research Priorities (Table 1). Offerors whose freestanding Concept Paper did not receive a favorable evaluation will be notified by email regarding the outcome of high-level evaluation. Offerors whose freestanding Concept Paper will receive a favorable high-level evaluation will be forwarded on for an evaluation of a Full Proposal. Full Proposal will follow a scientific review process described in Part IV and will be evaluated by a panel of subject matter experts (technical evaluation panel).

OPTIONAL Early Concept Paper Submission and Review: Applicants may also submit a freestanding Concept Paper by 11:59 PM (Eastern Standard Time) on November 6th, 2023. Any Concept Paper received by this date will undergo a high-level evaluation for program alignment with FDA priorities and mission. Offerors whose freestanding Concept Paper will receive a favorable high-level evaluation will be recommended for Full Proposal Submission. Offerors receiving a recommendation to submit a Full Proposal may submit a freestanding Concept Paper along with a freestanding Full Proposal on or before February 19th, 2024 for FY24 funding consideration. Offerors that do not receive a recommendation for Full Proposal submission may still consider submitting a revised or new freestanding Concept Paper along with a freestanding Full Proposal on or before February 19th, 2024 for FY24 funding consideration.

Stage 2: This stage will only be initiated if the technical evaluation panel recommends revisions to the Full Proposal after the Full Proposal has undergone scientific review. The Offeror will have thirty (30) days from the date of revision request (from FDA) to submit a revised Full Proposal.

Notification to Offerors: All Offerors will receive an email acknowledging receipt of their freestanding Concept Paper and freestanding Full Proposal submission. Debriefings for Concept Paper and Stage I Full Proposal will not be provided; however, general feedback may be provided in the response letter from FDA. If needed, Offerors shall be contacted via email to clarify information provided in the Full Proposal. Offerors will be requested to respond within the timeline specified in the email. Full Proposal will not be accessed for applications whose Concept Paper did not receive a favorable evaluation.

Successful Offerors: Offerors whose Full 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.

Table 2: Submission deadlines for FY24 BAA

Deadline for submission#	**Description**	**What to submit?**	**How to Submit?**	**What to expect?**
11/6/2023	Optional Early Concept Paper Submission	Free standing Concept Paper (attachment 4)	~Email subject line "Charge Area_FDABAA-24-00123 Optional Early Concept Paper"	FDA recommendation for interest or lack of interest of Full Proposal submission
2/19/2024	Stage I Submittal Packages for FY24 funding consideration	Checklist (attachment 3), Freestanding Concept Paper (attachment 4), $Freestanding Full Proposal	~Email subject line "Charge Area_FDABAA-24-00123 Concept Paper with Full Proposal"	Evaluate Concept Paper and forward Full Proposal of favorable Concept Papers for review

			%~Email subject line "BAA Number_ Concept Paper with Full Proposal"	Review Full Proposal
*2/20/2024-9/30/2024	*Stage I Submittal Packages for open period	*Same as above	*Same as above	*Same as above
Within 30 calendar days of FDA request^	Stage II: Revised Full Proposal Submittal Package	Cover Page, Response summary to feedback, Revised Full Proposal	~Email subject line "BAA Number_Revised Full Proposal"	Review of responses and revised Full Proposal

All submission deadlines indicate 11:59 PM (Eastern Standard Time)
~FDABAA@fda.hhs.gov
$Freestanding Full Proposal: Volume I Technical Proposal with appendix (attachment 5) and Volume II Cost Proposal with appendix
%Optional Early Concept Paper with FDA recommendation for Full Proposal submission
*Open Period: Stage One Submittal Packages received after February 19, 2024 will still be accepted, but due to a lack of lead time and funding availability may not be considered for award in FY24. These submissions may be considered for award in FY25.
^Unless designated otherwise by the Contracting Officer

Section 2: Stage 1 Concept Paper and Full Proposal

Preparation of Concept Paper: Interested Offerors shall submit a freestanding Concept Paper. The Concept Paper will be evaluated to conduct a High-Level review to determine potential program alignment with FDA priorities and mission.

1. All Concept Papers shall be submitted using the template provided in attachment 4. The *Concept Paper* template comprises of **Concept Paper Cover Page (sample below)** and **Concept Paper Overview** sections. Complete all fields of both sections of the Concept Paper. Incomplete Concept Paper submissions will **not be evaluated and shall be disqualified from consideration**.

Project Title: FY24 BAA Concept Paper Cover Page Sample	
Charge Area: I. modernize development and evaluation of FDA regulated products	**Regulatory Science Topic Area of Interest**: C. Analytical and Computational Methos
FDA Regulated Areas: Devices	**Demographics and Populations**: none

Primary Research Area: I.C.3.a.	**Secondary Research Area**: I.F.4.b.
Offeror: John and Smith Technological Institute	**Offeror Contact Information**: **Name**- John Smith, PhD **Email**- John.Smith@email.com; John.Smith@uofsmith.com **Phone**-111-111-1111
Principal Investigator: John Smith	**Affiliations**: The University of Smith
Research and Development Justification: Proposed research qualifies as applied research (See FAR 35.001). Objective of the proposal is to describe the FY24 BAA application process.	
Between 10/3/2023 to 11/6/2023, has the Offeror submitted an Optional Early Concept Paper for FY24 BAA? Yes. **If Yes**, **Primary Research Area:**II.B.7.e; **Status: FY24C2BWP7,** Recommended for Full Proposal	

2. Concept Paper content shall adhere to the page limit, format, and request for information.
   a. Page Size: 8 ½ x 11 inches; Spacing – single; Margins – 1 inch; Font – Arial; Font Size – 12
   b. Page limit: Three (3) pages. **If the submission exceeds the number of pages specified, only the pages up to the limit will be reviewed.**
   c. Provide information for Concept Paper Cover Page and Concept Paper Overview to state the Research Strategy (Aims, Methods, Considerations); Regulatory Science Impact; Proposed Deliverables and Funding (See attachment 4)
   d. Single PDF formatted file as an email attachment
   e. 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.
   f. All freestanding Concept Paper submissions must be UNCLASSIFIED.

3. Optional Early Concept Paper Submission: If the applicant is interested in submitting an Optional Early Concept Paper on or before 11:59 PM (Eastern Standard Time) of November 6th, 2023, a freestanding Concept Paper shall be emailed directly to the following email address: FDABAA@fda.hhs.gov. Do not send to any other FDA email. Include "Charge Area_ FDABAA-24-00123 Optional Early Concept Paper" in the email subject line. Offerors must select a primary charge area to submit the Concept Paper under, even if the submission qualifies for multiple research charge areas. FDA shall not be responsible for email delivery exceptions or communications sent to unmonitored email folders. All submissions after this date **must submit a Freestanding Concept Paper and freestanding Full Proposal.**

4. Freestanding Concept Paper and freestanding Full Proposal shall be emailed directly to the following email address: FDABAA@fda.hhs.gov. Do not send to any

other FDA email. Include "Charge Area_ FDABAA-24-00123 Concept Paper with Full Proposal" in the email subject line. Offerors must select a primary charge area to submit the Concept Paper under even if the submission qualifies for multiple research charge areas. FDA shall not be responsible for email delivery exceptions or communications sent to unmonitored email folders.

Preparation of Full Proposal: In addition to the freestanding Concept Paper, interested Offerors shall submit a freestanding Full Proposal. With a favorable high-level evaluation of the Offeror's Concept Paper, the Offeror's Full Proposal will be forwarded for a scientific review by a panel of subject matter experts. The Full Proposal expands on the information provided in the freestanding Concept Paper. Full Proposal must be prepared as two separate volumes: Volume I Technical Proposal and related Appendices and Volume II Cost Proposal and related Appendices. 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.

Preparation of Volume I – Technical Proposal
All Technical Proposals shall be submitted using the template provided in attachment 5.

1. All Volume I – Technical Proposals must be submitted using the template provided. Complete all fields of the Full Proposal Paper. Incomplete Full Proposal Paper submissions **may result in increased review time and cannot be considered for FY24 funding.**

2. Volume I – Technical Proposal content shall adhere to the page limit, format, and request for information.

a. Page Size: 8 ½ x 11 inches; Spacing – single; Margins – 1 inch; Font – Arial; Font Size – 12

b. Page limit: The technical proposal page limit is 50 pages (page limitation for items iv-xi listed below) including figures, tables and graphs unless otherwise specified by the Contracting Officer. **If the submission exceeds the number of pages specified, only the pages up to the limit will be reviewed.** Provide information for

i. Cover page
ii. Official Transmittal letter
iii. Table of contents
iv. Executive Summary
v. Research and Development Justification
vi. Scientific and Technical Information (overview of the proposal, research methods and approach)
vii. Regulatory Science Impact (relevance, research and development justification, impact)

viii. Resources Proposed (personnel, licensure, and agreements, regulatory or compliance approvals, communication management plan)
ix. Gantt Chart, Work Breakdown Structure and Milestones
x. Deliverable Schedule
xi. Risk mitigation plan
xii. Security Planning
xiii. Intellectual Property
xiv. Bibliography/References

c. Single PDF formatted file as an email attachment
d. 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.
e. All Full Proposal Paper submissions must be UNCLASSIFIED.

3. 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). Additional specific information to be included is referenced below and attachment 5. 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
Biographical sketches/ Resumes/Roles and Responsibilities	Yes	See attachment 5
Intellectual Property	Yes	See attachment 5. https://www.acquisition.gov/far/52.227-11; https://www.acquisition.gov/far/52.227-14; https://www.acquisition.gov/far/52.227-17
Statement of Work	Yes	See attachment 6
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. See Part III, Section 6. http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf
Animal Use	If Applicable	See Part III, Section 7
Use of Select	If Applicable	See Part III, Section 9 http://www.cdc.gov/od/sap; USDA

Agents		Select Agent and Toxin List; USDA Select Agent Services
Laboratory License Requirements	If Applicable	See Part III, Section 10
Security	If Applicable	
Good Laboratory Practice (GLP) Compliance	If Applicable	
Good Manufacturing Practice (GMP) Compliance	If Applicable	
Good Clinical Practice (GCP) Compliance	If Applicable	

4. Restrictive markings on Technical Proposal: 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 in attachments (list attachments).*

Preparation of 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 Stage II revised Full Proposal invite 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.

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. Requested Contract Type (Cost or Firm-Fixed-Price. Note, cost type contract proposals will be given preference)
    a. For Firm-Fixed-Price Contracts only, please include a discussion that addresses:
        i. How the effort is capable of being priced in advance with any level of

certainty; and

ii. Whether or not performance-based payments (PBP) [i.e., progress payments] are being sought

- If not, please understand that invoicing will only be allowable at the completion and acceptance of full contract performance.
- If so, please provide the key milestones for which (PBP) are being requested Note:
- PBPs must be meaningfully tied to contract progress (e.g., the submittal of a monthly report does not qualify).
- As a general rule, PBPs may not generally exceed 80% of the total contract value for any resultant award made under this announcement.

b. For Cost Reimbursement contracts, consider using the Preaward Survey-Accounting System Checklist (appendix 8 available on sam.gov) to provide information regarding your accounting system.

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. The Contractor shall use the cost proposal template (attached as Appendix 7). The cost proposal 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:

1. 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.

2. 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.

3. 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;

4. 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.

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

b. 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, 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.

1. Fee/profit including percentages.

2. Certified Cost and Pricing Data (see FAR 15.403-4(a)(1)) shall be provided for proposals over $2M.

3. Data Other Than Certified Cost or Pricing Data (see FAR 15.403-3) shall be provided for proposals under $2M.

Preparation of 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 Stage II revised 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 $750K 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	If Applicable	http://oamp.od.nih.gov/sites/default/files/DGS/contracting-forms/Govt-Owned-

	Held Property		Prop.pdf		
7	Cost Proposal Template	Optional	Attachment on www.sam.gov		
8	Preaward Survey-Accounting System Checklist	Optional	Attachment on www.sam.gov		

Submission of Full Proposal:

1. If Optional Early Concept Paper recommended for Full Proposal submission, freestanding Concept Paper and freestanding Full Proposal shall be emailed directly to the following email address: FDABAA@fda.hhs.gov. Do not send to any other FDA email. Include "BAA Number_Concept Paper with Full Proposal" in the email subject line. Offerors must select a primary charge area to submit the Concept Paper under even if the submission qualifies for multiple research charge areas. FDA shall not be responsible for email delivery exceptions or communications sent to unmonitored email folders.

2. If Optional Early Concept Paper not submitted by applicant, a freestanding Concept Paper and freestanding Full Proposal shall be emailed directly to the following email address: FDABAA@fda.hhs.gov. Do not send to any other FDA email. Include "Charge Area #_ FDABAA-24-00123 Concept Paper with Full Proposal" in the email subject line. Offerors must select a primary charge area to submit the Concept Paper under even if the submission qualifies for multiple research charge areas. FDA shall not be responsible for email delivery exceptions or communications sent to unmonitored email folders.

3. Any submission after 11:59 PM (EST) of November 6, 2023 must submit a checklist (see attachment 3), three (3) pages freestanding Concept Paper (see attachment 4), freestanding Full Proposal* that comprises of Volume I Technical Proposal with appendix (see attachment 5) and Volume II Cost Proposal with appendix. If submissions exceed page limitations, only those pages previously defined will be reviewed. ***Additionally, please know:***

   a. Any application submitted after 11/6/2023 without a freestanding Full Proposal will be considered incomplete and will not be considered for

review process.

b. Multiple submissions on the same topic or closely related topics are discouraged.

*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.

Section 3: Stage 2 Revised Full Proposal

With a successful review of the Offeror's Full Proposal, the Offeror may either be requested to submit a revised Full Proposal or may be notified of the review outcome for intent to award or reject). The revised Full Proposal must be prepared to address feedback provided by FDA for Volume I Technical Proposal (and appendix), Volume II Cost Proposal (and appendix), and/or information to address clarifications from FDA. The Offeror will have 30 days from the date of revision request letter to submit a revised Full Proposal. The revised Full Proposal shall include:

1. Cover Page with
    i. BAA Number
    ii. Title of proposal
    iii. Primary Offeror Name
    iv. Technical contact (name, address, phone/fax, electronic mail address)
    v. Administrative and/or business contact (name, address, phone/fax, electronic mail address)
    vi. Date revised submission request letter received
2. Explanation with summary of response to FDA's feedback and/or concerns and how was the feedback and or concern addressed within the revised Full Proposal with references to page numbers of the revised version.
3. Revised Full Proposal

Revised Full Proposals* must be emailed to FDABAA@FDA.HHS.GOV by the date specified in the letter. Include "BAA Number_Revised Full Proposal" in the email subject line. If the revised Full Proposal attachments exceed the size limitation for email the Offeror shall contact the contracting officer to arrange for other delivery methods.

*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.

Section 4: Withdrawal of Full 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 revised Full Proposal.

Section 5: 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.

Section 6: Studies That Involve Human Subjects

All research under this BAA must address the involvement of human subjects and protections from research risk related to their participation in the proposed research plan and comply with 32 CFR 219, 10 U.S.C. 980, and, as applicable, 21 CFR Parts 11, 50, 54, 56, 312) (45 CFR

Part 46) and the ICH as well as other applicable federal and state regulations. HHS Policy also requires that women and members of minority groups and their subpopulations: children and the elderly (pediatric and geriatric) must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification is provided with respect to the health of the subjects or the purpose of the research. The HHS policy on studies that involved human subjects can be accessible through the HHS website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

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

The Food and Drug Administration Amendments Act of 2007 (FDAAA) contains provisions that expand the current database known as ClinicalTrials.gov to include additional requirements for individuals and entities who are involved in conducting clinical trials that involve products regulated by FDA or that are funded by the Department of Health and Human Services (HHS), including FDA. These additional requirements include mandatory registration of certain types of clinical trials, as well as reporting of results for certain trials (“applicable trials”) for inclusion in the ClinicalTrials.gov database. More detailed information on the definition of "applicable clinical trial" and the registry and results reporting requirements can be found at https://clinicaltrials.gov/ct2/manage-recs/fdaaa.

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

be signed by the contractor and cosigned by the institutional official,and sent to the COR and the contracting officer (CO). More detailed information on the definition of "applicable clinical trial" and the "responsible party" can be found at http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf.

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

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

i. 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.

ii. 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.

iii. 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.**

iv. 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.

v. 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.

vi. 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.

vii. 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)

i. 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 subject in accordance with 45 CFR part 46 and the Assurance of Compliance.

ii. 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.

iii. 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).

iv. 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)

i. 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.

ii. 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.

iii. After the contract has been awarded, the Contractor shall take the following actions:

a) 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.

b) 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.

iv. 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.

v. 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.

vi. 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.

vii. 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:

i. The creation of a human embryo or embryos for research purposes; or

ii. 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)).

a) 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.

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

352.211-3 Paperwork Reduction Act (DEC 2015)

i. 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.

ii. 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 300 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.

Section 7: 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:

i. 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.

ii. 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.

iii. Provide information on the veterinary care of the animals involved.

iv. Describe the procedures for ensuring that discomfort, distress, pain, and injury will

v. 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.

vi. 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.

***Section 8: 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.

Section 9: 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.

Section 10: 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.

Section 11: 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.

Section 12: Advanced Understandings

i. 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.

ii. 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

iii. Press Releases: The Contractor agrees to accurately and factually represent the work conducted under this contract in all press releases. Misrepresenting contract results or releasing information that is injurious to the integrity of FDA may be construed as improper conduct. Press releases shall be considered to include the public release of information to any medium, excluding peer-reviewed scientific publications. The Contractor shall ensure that the Project Officer has received an advance copy of any press r5e0lease related to this contract not less than four (4) working days prior to the issuance of the press release.

iv. 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).

v. 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.

a) 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.

b) 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.

c) 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.

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

Section 13: 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.

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

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

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

ii. 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.

iii. 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.

iv. 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.

v. 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.

vi. 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.

vii. 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 14: General Information

i. CLASSIFIED SUBMISSIONS: Classified proposals will not be accepted.

ii. 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.

iii. 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.

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

Part IV: Proposal Evaluation

A. Evaluation Criteria:

The selection of one or more sources for award will be based on an evaluation of each Offeror's Concept Paper (High-Level Program Relevance evaluation) and Full Proposal (Stage I and Stage II). After receiving an Offerors' Concept Paper and Full Proposal Submission, the FDA will conduct a High-Level review of the Concept Paper to determine potential program relevance. If the submission is determined to have the potential to align with an Agency Program, the Full Proposal will be forwarded for a full Stage I Evaluation. Both Stage I proposals and Stage II proposals (for Stage I Offerors requested to submit a revised 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):

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

Table 3: Overview of BAA Application Process

Step	Process	Communication
Optional Early Concept Paper Submission	-Applicants submit Freestanding Concept Paper to FDABAA@fda.hhs.gov -All submissions due by 11:59 PM (EST), November 6th, 2023	-FDA to notify applicants receipt of documents via email -Notify recommendation for interest or lack of interest for Full Proposal submission -Clarify information with applicant via email
Submission	-Applicants submit Freestanding Concept Paper and Freestanding Full Proposal to FDABAA@fda.hhs.gov -All submissions for FY24 funds consideration due by 11:59 PM (EST), February 19th, 2024 for FY24 funding consideration (includes Full Proposal recommended for optional, early Concept Paper submissions)	- FDA to notify applicants receipt of documents via email -Clarify information with applicant via email
Stage I	-FDA Program Leaders shall conduct a High-Level review to determine potential program relevance of Freestanding Concept Paper. -If favorable evaluation of Concept Paper, proceed with Full Proposal Review by Subject Matter Experts following the evaluation criteria -If unfavorable evaluation of Concept Paper, Full Proposal will NOT be reviewed, and applicant will be notified of the decision	-FDA to notify applicants unfavorable evaluation of Concept Paper -For favorable Concept Paper evaluations, FDA to request applicants to either submit revised Full Proposal based on the feedback provides or communicate decision (intent to award or reject) via email -Seek clarifications from applicant via email
Stage II	-Applicants requested to submit a revised Full Proposal to FDABAA@fda.hhs.gov within 30 days of receipt date. -Revised Full Proposal reviewed by Subject Matter Experts	-Communicate decision (intent to award/reject) via email -Seek clarifications from applicant via email

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.

1. 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.

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

    a. Decisions to release proposals outside the Government for evaluation purposes shall be made by the agency head or designee;

    b. 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;

    c. 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;

    d. 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

    e. 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.

5. 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: FY24 BAA Application Checklist

Proposal Title:
Primary Offeror:
Technical contact: name, address, phone/fax, electronic mail address
Administrative and/or Business contact: name, address, phone/fax, electronic mail address

As described in Part I of this announcement:
Charge Area: ☐ Charge I ; ☐ Charge II; or ☐ Charge III
Regulatory Science Topic Area of Interest: ☐ A ; ☐ B; ☐ C; ☐ D ; ☐ E; ☐ F; ☐ G ; ☐ H; ☐ I; ☐ J ; or ☐ K;
FDA Regulated Areas:
Demographic and/or Populations:

CHECKLIST	COMMENTS
☐ **CONCEPT PAPER**	Required
☐ **VOLUME I – TECHNICAL PROPOSAL**	Required
☐ **VOLUME I – TECHNICAL PROPOSAL APPENDIX**	Required
☐ **VOLUME II – COST PROPOSAL**	Required
☐ **VOLUME II – COST PROPOSAL APPENDIX**	
☐ **STATEMENT OF WORK (SOW)**	Required
☐ **SUPPLEMENTARY MATERIAL 1**	Provide description
☐ **SUPPLEMENTARY MATERIAL 2**	Provide description
☐ **OTHER**	Provide description

Attachment 4: FY24 BAA Application Concept Paper Template

I. Concept Paper Cover Page:

Project Title:	
Charge Area:	**Regulatory Science Topic Area of Interest**:
FDA Regulated Areas:	**Demographics and Populations**:
Primary Research Area:	**Secondary Research Area**:
Offeror:	**Offeror Contact Information**: **Name-** **Email-** **Phone-**
Principal Investigator:	**Affiliations**:
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). All acquisitions resulting from this announcement must meet one or more of the FAR definitions for basic research (See FAR 2.101(b)(2)), applied research (See FAR 35.001) and development (See FAR 35.001). Include a brief and clear justification describing how the project falls under the FAR requirements for R&D work.	
Between 10/3/2023 to 11/6/2023, has the Offeror submitted an Optional Early Concept Paper for FY24 BAA? Yes/No. **If Yes**, state **Primary Research Area** (i.e, II.B.7.e) and **Status** of previous submission (i.e., Recommended for Full Proposal (BAA Number provided), Not Recommended for Full Proposal, Unknown).	

II. Concept Paper Overview

1. **Research Strategy**:
   a. **<u>Aims</u>:** Succinctly list the **specific objectives of the proposed research** (State the problem/objective and provide motivation for addressing that problem/objective) and **primary scientific challenges being addressed**

   b. **<u>Methods</u>:** Clearly **describe the approach**, **description of level of effort, and the nature as well as extent of the anticipated results of the effort** (one Figure that is a 508 compliant picture or graphic that illustrates the research or concept can be included)

   c. **<u>Considerations</u>: Brief description of the Offerors intellectual property ownership, data ownership, or licensure**; **statements on work experience for similar effort with FDA or another agency**

2. **Regulatory Science Impact**
    a. How does this research address an unmet need or fill a critical knowledge gap to advance regulatory science and the program's priorities? How might FDA apply the research findings to the development of new tools, approaches, or standards? Please explain the benefits of proposed technology and challenges and how the proposed project aligns with the objectives of FDA Regulatory Science

3. **Proposed Deliverables and Funding**
    a. List of the major goals, deliverables, or milestones and proposed funding by project year. Total proposed funding is the Base period cost plus each option period with no more than 5 years total.

Milestones	Timeline	Funding
Total Proposed Funding:		

Attachment 5: FY24 BAA Volume I Technical Proposal Template

	Volume I – Technical Proposal Checklist	
☐	1. Cover page	
☐	2. Official Transmittal Letter	
☐	3. Table of contents	
☐	4. Executive Summary	
☐	5. Research and Development Justification	
☐	6. Scientific and Technical Information	
☐	7. Regulatory Science Impact	
☐	8. Resources Proposed	
☐	14. Bibliography/References	
☐	Appendix	
	☐	Biographic sketches (required)
	☐	Intellectual Property (required)
	☐	Statement of Work (required)
	☐	Protection of Human Subjects (if applicable)
	☐	Animal Use (if applicable)
	☐	Use of Select Agents (if applicable)
	☐	Laboratory License Requirement (if applicable)
	☐	Security (if applicable)
	☐	Good Laboratory Practice (GLP) Compliance (if applicable)
	☐	Good Manufacturing Practices (GMP) Compliance (if applicable)
	☐	Good Clinical Practice (GCP) Compliance (if applicable)

A. Volume I – Technical Proposal (Fifty [50] page limit for items 4 to 11)

1. Cover page:
    a. BAA number (if provided by the FDA BAA Team), Charge Area, Regulatory Science Topic Area of Interest, FDA Regulated Areas, and/or Demographic and Populations (as described in Part I of this announcement)
    b. Title of proposal
    c. Primary Offeror and complete list of subcontractors and/or affiliations, if applicable
    d. Technical contact (name, address, phone/fax, electronic mail address)
    e. Administrative and/or business contact (name, address, phone/fax, electronic mail address)

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: Provide a synopsis of the proposal to include research rationale, hypotheses to be tested; short description of the research design, method, and/or approach; primary and secondary objectives; primary and secondary outcomes; duration of the proposed study; importance of the study; regulatory research impact of the proposed study as perceived by the applicant

5. 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.** Include a clear justification describing how the project falls under the FAR requirements (announcement must meet one or more of the FAR definitions for basic research–See FAR 2.101(b)(2)), applied research–See FAR 35.001, and development–See FAR 35.001) for Research and Development work.
    a. 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))
    b. 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).
    c. 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).

6. Scientific and Technical Information:

    a. Overview of the proposal
        i. Introduction and background to discuss (with reference citations) relevant literature to address rationale for research and/or issues or

controversies, concise up-to-date status of the field, relevant current context of the study and gaps in current knowledge, significance of the study.

ii. State all aims, goals, objectives, and proposed outcomes. Discuss hypothesis to be tested and/or research questions to be addressed.

iii. Degree of innovation of the approach and potential to offer a revolutionary increase in capability after implementation.

b. Research Methods and Approach: Provide clear and detailed description of overall research method, approach, and/or design, include scientific justification or rationale for the research design, method, and/or approach with reference citations, discuss the PD/PI's preliminary studies, data, and/or experience pertinent to this proposal. Provide clear information and attach supporting material as Appendix for:

i. Proposed Population, Biospecimens, and/or data such as study population; type and source; exclusion and inclusion criteria; time points for exposure and measurements; endpoints; dosing and administration with justification; recruitment, retention, and follow-up strategies; screening procedures; details for preparation, handling, storage, accountability, formulation, packaging, storage, and/or stability.

ii. Proposed assessments, evaluations, and/or procedures such as statistical considerations (sample size and determination rationale, hypotheses, statistical analysis plan); measures for bias minimization; validation; quality control; data collection; safety assessments

iii. Proposed regulatory, operational, and/or safety considerations such as informed consent; confidentiality and privacy; safety oversight; quality assurance, control, and monitoring; specimens and/or data management (collection, storage, access, sharing, handling, disposition, record keeping); plan for seeking approvals (e.g., IRB, PRA); compliance statements (GMP, GCP, GLP)

7. Regulatory Science Impact:

a. Relevance to the BAA program regulatory research areas of interest indicated in Table 1: Explain research alignment with the priorities and relevant scientific initiatives at FDA, benefits of proposed technology and challenges.

b. Impact: Describe regulatory impact of research proposed. How does this research address an unmet need or fill a critical knowledge gap to advance FDA regulatory science? How might FDA apply the research findings towards advancement of regulatory research?

8. Resources Proposed:

a. Personnel with role, responsibilities, field of expertise, expectations,

experience overview, and efforts. Provide list of key personnel. Attach resumes and CV as appendix

b. Licensure and agreements with sub-contractors, collaborators, and/affiliations proposed to work on the project, nature of agreements (Service Level Agreements, Letter of Intent, and/or any other formal agreements showing commitment for research participation). Provide details in appendix.
c. Requirement for any regulatory or compliance approvals (IRB, PRA, MTA, etc.). Provide details in appendix.
d. Communication management plan with ways of communication, frequency of communication, stakeholders identified for communication, extent of collaboration intended with FDA subject matter experts, research dissemination and information sharing, publications.

9. 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.

10. 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.

11. Risk mitigation plan: Identify and list of known potential risks and a mitigation plan to address risks.

12. 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 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

13. 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.

14. Bibliography/References: Applicants should follow scholarly practices in providing citations for source materials relied upon when preparing any section of the application.

B. Volume I – Technical Proposal 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 twenty (20) pages. Note that biographical sketches/resumes are not included in this page limitation. 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.

1. Biographical sketches/ Resumes/Roles and Responsibilities
    a. Required: Yes
    b. 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.
    c. 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 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.

2. Intellectual Property
    a. Required: Yes
    b. https://www.acquisition.gov/far/52.227-11; https://www.acquisition.gov/far/52.227-14; https://www.acquisition.gov/far/52.227-17

3. Statement of Work (SOW)
    a. Required: Yes
    b. 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.

c. The Offeror shall identify whether or not the proposed effort constitutes a non-severable, single, indivisible undertaking, or if the tasks/aims can be separated 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. 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.
d. 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 (See attachment 6).
e. 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.
f. 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. Encourage inclusion of detailed justification of costs that are tied to the milestones or deliverables (especially if a multi-year proposal).
g. See Attachment 6

4. Protection of Human subjects
    a. Required: If applicable. If not Applicable, provide justification.
    b. 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
    c. See Part III, Section 6 of announcement for details

5. Animal Use
    a. Required: If applicable. If not Applicable, provide justification.
    b. See Part III, Section 7 of announcement for details

6. Use of Select Agents
    a. Required: If applicable. If not Applicable, provide justification.
    b. See Part III, Section 9 of announcement for details
    c. https://www.selectagents.gov/

7. Laboratory License Requirements
    a. Required: If applicable. If not Applicable, provide justification.
    b. See Part III, Section 10 of announcement for details

8. Security
    a. Required: If applicable. If not Applicable, provide justification.

9. Good Laboratory Practice (GLP) Compliance
    a. Required: If applicable. If not Applicable, provide justification.

10. Good Manufacturing Practice (GMP) Compliance
    a. Required: If applicable. If not Applicable, provide justification.

11. Good Clinical Practice (GCP) Compliance
    a. Required: If applicable. If not Applicable, provide justification.

Attachment 6: FY24 BAA Application Statement of Work Template

It is anticipated that the proposed SOW will be incorporated as an attachment to the resultant award instrument. The SOW, without restrictive markings, is your company's affirmation that the SOW is non-proprietary and releasable in response to Freedom of Information Act (FOIA) requests.

At a minimum, the format and content of the Statement of Work should contain the following information. If options are included, separate sections should be included to address what work will occur in the base and each option period.

TITLE OF PROGRAM/SERVICES AND/OR SUPPLIES

1.0 Scope. This section should describe, in general terms, the work effort that will be performed by the contractor.

2.0 Requirements. *This section must describe each task(s) the contractor shall perform using complete sentences, active voice, and mandatory terms ("the contractor shall"). The task(s) shall be arranged systematically and logically so that both parties (contractor and government) understand the desired effort. All task(s) must be listed in chronological order. The task(s) must be explained in clear and understandable terms. Include any industry specific standards that need to be adhered to in fulfilling the SOW.*

(NOTE: Numbering of tasks shall be as follows 1.1, 1.2, 1.3, 2.1, 2.2, 2.3, etc.)

3.0 Deliverables. *Deliverable product(s) could consist of, but not limited to, monthly or quarterly progress report (technical and financial), final report, software (executable, source, or operational code), and hardware (contractor acquired property, government furnished property, prototypes). In this section all of the deliverable items should be defined.*