

Center for Biologics Evaluation and Research

**STRATEGIC PLAN FOR
REGULATORY SCIENCE AND RESEARCH**

2012-2016



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Opening Statement from the Center Director

The Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) plays a leading role in the development of therapies that will become the standard of care in the 21st Century, both in the United States and around the world. These emerging therapies include a wide variety of biologic products, such as those for gene replacement and tissue regeneration. In addition, novel strategies and approaches may be employed for developing new vaccines. CBER plays a significant role in maintaining a safe and adequate supply of blood and blood products.

To meet these challenges, CBER's regulatory science and research program must provide the environment to facilitate the development of new biological products and evaluate them for safety and effectiveness. Biological products may have great complexity and diversity of structure and function; are vulnerable to contamination; are inherently difficult to manufacture; and have the potential for long-term adverse effects of treatment. These challenges require that CBER's regulatory science and research program supports CBER reviewer decisions so that they may be at the forefront of the underlying research fields that drive the development of these biologic products and the evolving technology designed to evaluate them.

The development of the CBER Strategic Plan for Regulatory Science and Research is based on the CBER mission and Strategic Plan¹. The CBER Strategic Plan for Regulatory Science and Research also supports FDA's Strategic Plan for Regulatory Science and ongoing FDA research initiatives (Refer to Appendix A for additional details.)

The CBER Strategic Plan for Regulatory Science and Research provides an overview of CBER's regulatory environment addressing the challenges of regulating biologics, the researcher-reviewer model used in CBER, and a description of the CBER's Research Management program. This information will provide an explanation and context for understanding CBER's research strategic goals, objectives, and strategies.

The CBER Strategic Plan for Regulatory Science and Research details the types of research programs needed to address the challenging regulatory issues CBER will face in the next several years. The plan also describes the technology and infrastructure required to meet those needs and the steps we will take to put those resources to use efficiently and effectively.

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¹ The CBER Strategic Plan may be accessed by the CBER Internet link (<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/UCM266867.pdf>)

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CBER Mission

To ensure the safety, purity, and potency, of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through our mission, we also help to defend the public against the threats of emerging infectious diseases and bioterrorism.

In fulfilling our mission as a Center in the U.S. Food and Drug Administration, we apply the following principles with the highest ethical standards and integrity:

- Develop, maintain, and support a high-quality and diverse workforce
- Ensure compliance with laws and regulations through review, education, surveillance, and enforcement
- Conduct research as an essential element of science-based decision-making

CBER Strategic Goals²

CBER's Strategic Plan has six strategic goals covering four programmatic and two supporting areas. These goals are the following:

1. Increase the nation's preparedness to address threats as a result of terrorism, pandemic influenza and emerging infectious diseases
2. Improve global public health through international collaboration including research and information sharing
3. Enhance the ability of advances in science and technology to facilitate development of safe and effective biological products
4. Ensure the safety of biological products
5. Advance regulatory science and research
6. Manage for organizational excellence and accountability

CBER Regulatory Environment

The challenge of regulating a diverse and complex group of biologic products is addressed with the CBER researcher-reviewer model. The CBER Research Management Program ensures that the contributions based upon individual expertise facilitated by use of the researcher-reviewer model meet CBER's objectives and support FDA's Advancing Regulatory Science Initiative.

1. Challenges of Regulating Biologics

CBER regulates a wide variety of complex biologic products (Figure 1) that differ significantly from chemically synthesized drugs. These products include blood, blood components and blood products, test kits used to screen blood and tissues for infectious agents, vaccines, allergenic products, tissues, and cutting-edge medical products such as cell and gene therapies. These products address critical public

² Four of CBER's Strategic Goals are the same as long-term objectives contained in the FDA Strategic Priorities (2011 – 2015) under the FDA's strategic goal entitled, "Promote Public Health by Advancing the Safety and Effectiveness of Medical Products – Advance Biologics Safety and Effectiveness." See page 2 for the Internet link for accessing the CBER Strategic Plan.

health needs, such as prevention of childhood mortality and morbidity from infectious disease through licensure of safe and effective vaccines; life-saving treatments that require blood, blood components, and blood products; novel ways of treating chronic diseases, including metabolic disorders, cancer, diabetes, and neurologic disorders; and enabling wound healing and other types of tissue regeneration.

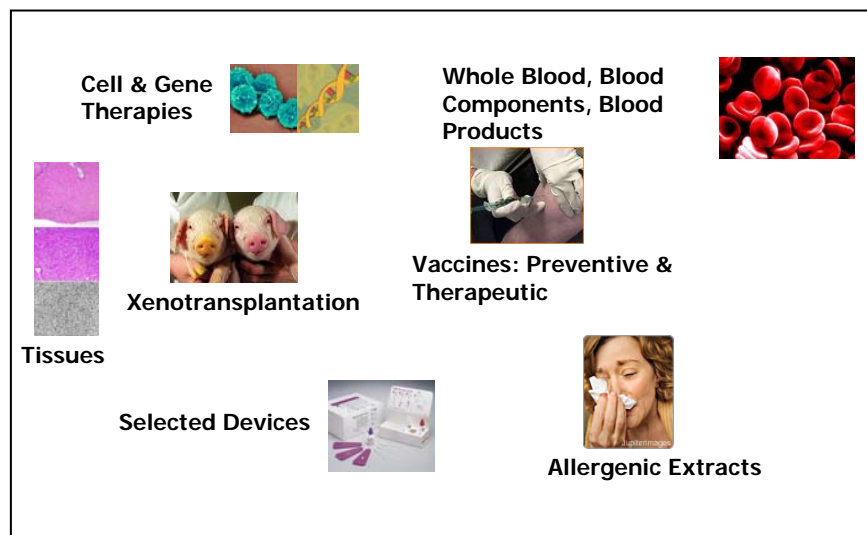


Figure 1. CBER regulates diverse and complex products.

CBER-regulated products pose four significant regulatory challenges that reflect both the rapid pace of biomedical research and the nature of the products the center regulates:

- **Complexity and diversity:** Biologics are complex and diverse, and often incorporate new scientific knowledge. CBER reviewers must have an in-depth understanding of the technology used to prepare them, and when feasible, knowledge of the mechanism of action
- **Vulnerability to contamination:** Biologic source materials used to manufacture products (e.g., mammalian cell lines) and the source of the product itself (e.g., blood from human donors) are particularly vulnerable to contamination with infectious agents
- **Processing difficulties:** Biologics cannot withstand common purification and decontamination methods, and thus require rigorous control of the source materials, manufacturing processes, and sensitive and specific safety, potency, and purity testing
- **Long-term adverse effects of treatment:** Some biological products, for example certain infused cells or integrating viral vectors, have the potential to persist long-term in the body. Some types of adverse events, which might include cancer, may take years to occur, and understanding how to monitor and clinically respond to such adverse events poses unique challenges

To address these challenges, CBER scientists and reviewers have expertise in testing and evaluating the risks associated with different source materials. They also must proactively develop standards, reference materials, and validated methods for testing safety, potency, and purity. CBER also conducts risk-benefit analyses of products and establishes careful surveillance for adverse events that might be caused by biological products.

2. CBER Researcher-Reviewer Model Supports Development of Safe and Effective Products

CBER researchers working at the frontier of biomedical innovation and discovery contribute critical knowledge and expertise that supports the center's mission. This also gives the center expertise in the new technologies and classes of biologicals being developed by industry.

CBER makes efficient use of limited resources in addressing high priority scientific questions of regulatory importance by relying on both full-time reviewers and researcher-reviewers. The latter are scientists who have both regulatory responsibilities and conduct mission-related research. This combination of regulatory and research expertise enables CBER to play critical roles in:

- Identifying and solving problems affecting development of new product classes
- Characterizing and developing appropriate models for predictive pre-clinical testing of biological products under development, many of which are complex and novel
- Developing testing methods, reference materials, or other tools, to evaluate product safety and efficacy
- Identifying and implementing efficient new technologies for testing the safety and quality of currently licensed products
- Identifying actual or potential safety or efficacy problems with a new biological product that might not be obvious to the manufacturer
- Sharing new knowledge by making presentations at public conferences and publishing research results in peer-reviewed scientific journals, thus facilitating development of products

3. CBER Research Management Program

CBER coordinates its regulatory science and research efforts through Associate Directors for Research (ADRs) who work both in the Office of the Center Director and within each office that has a research component. The offices that have a research component are the Office of Vaccines Research and Review, the Office of Blood Research and Review, the Office of Cellular, Tissue and Gene Therapies, the Office of Biostatistics and Epidemiology, and the Office of Compliance and Biologics Quality. Appendix B provides an overview of CBER's organizational structure. The ADR at the center level develops center-wide policies and procedures to ensure that regulatory science and research programs of CBER are aligned with its regulatory mission. The office ADRs work closely with the center ADR to identify areas for development or improvement of policy and to implement these policies and procedures.

The Center Director and ADR administer a research management strategy that supports the overall goals of the regulatory science and research programs in order to ensure that research is relevant to our regulatory mission, is aligned with stated priorities, and represents productive, high quality science. Our research management strategy is supported by four “pillars” (Figure 3):

- 1) Strategic planning and priority setting
- 2) Appropriate allocation of resources
- 3) Researcher-Reviewer model
- 4) Internal and external evaluation to ensure quality, productivity, and regulatory and public health relevance



Figure 2. Four Pillars Supporting CBER’s Regulatory Science

Strategic Planning and Priority Setting

Each office uses a variety of sources to inform its strategic planning and priority-setting, including consideration of specific products under development but not yet submitted by the sponsor (horizon scanning). Typical sources include regulatory portfolio reviews; input from full-time review staff, researcher-reviewers, and office management; informal information gathering at scientific meetings; and formal external input from advisory committees, site visits, and workshops. Each office ADR synthesizes the input into specific research priorities, with broad research priorities at the center level reflecting office-specific priorities. Office ADRs also provide an annual research program report to the center ADR that includes a summary of the office’s regulatory portfolio (current and anticipated products), strategic planning for research programs, research priorities, and a summary of key scientific accomplishments from the prior year.

Appropriate Allocation of Resources

Office ADRs work with their respective office and division directors annually to evaluate all research programs within their office for regulatory relevance, productivity, and quality. To facilitate this review, CBER implemented an online reporting system requiring an annual progress report from each CBER researcher-

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reviewer that includes plans for the coming year. This evaluation informs the division and office directors during their annual allocation of research resources.

Office ADRs develop a budget proposal for each scientific program for the coming year based on the regulatory relevance, productivity, and quality. Following review and approval by office and division directors, the ADRs submit their reports to the center ADR. The center ADR and director review and approve the research program reports and proposed budgets to ensure consistency and fairness and to inform center-wide strategic planning for the research program.

Researcher-Reviewer Model

The use of researcher-reviewers enables CBER to maintain investigator-initiated research with input and oversight from CBER management. These researcher-reviewers also perform the same review activities as full-time review scientists, and thus are often the first to understand how to use their research skills and knowledge to address regulatory challenges and, when necessary, to respond in a timely manner to public health crises through laboratory investigations. The researcher-reviewer model enables CBER to rapidly focus limited research resources onto high-priority issues.

Internal and External Evaluation

CBER ensures accountability to its stakeholders through a combination of internal annual and cyclic evaluations, external scientific peer reviews, and input from a variety of external sources. Internal reviews include 1) annual management review of all research programs for relevance to priorities, quality, productivity, and feasibility; and 2) internal peer review of all researcher-reviewers at GS-13 or higher grade levels.

CBER also reviews its support to FDA research initiatives to ensure that research planning is incorporating these commitments and progress is being reported. CBER supports four FDA research initiatives: Critical Path, Advancing Regulatory Science, Nanotechnology Regulatory Science, and Medical Countermeasures. Appendix A provides a description of the FDA research initiatives and the CBER support provided.

External reviews include site visits for each laboratory unit every four years by an external panel of expert scientists working in the same scientific fields as the scientists under peer review, as well as periodic programmatic reviews through relevant advisory committees. For example, each product office has undergone programmatic reviews by an FDA advisory committee in the past five years, and in 2012-13, the center is scheduled for programmatic review of our research by the FDA Science Board.

With the direction set forth in the CBER Regulatory Science and Research Strategic Plan, CBER's regulatory science research program will be strengthened and enhanced to provide an important tool for supporting the science-based regulatory decisions and policy-making that facilitate the licensure of safe and effective products. Thus, this cross-cutting CBER Strategic Plan for Regulatory Science and Research plan provides a road map to implement FDA and CBER's commitment to advancing regulatory science and research. See the graphic below to show the role of

regulatory science and research in the development of biologics products development.

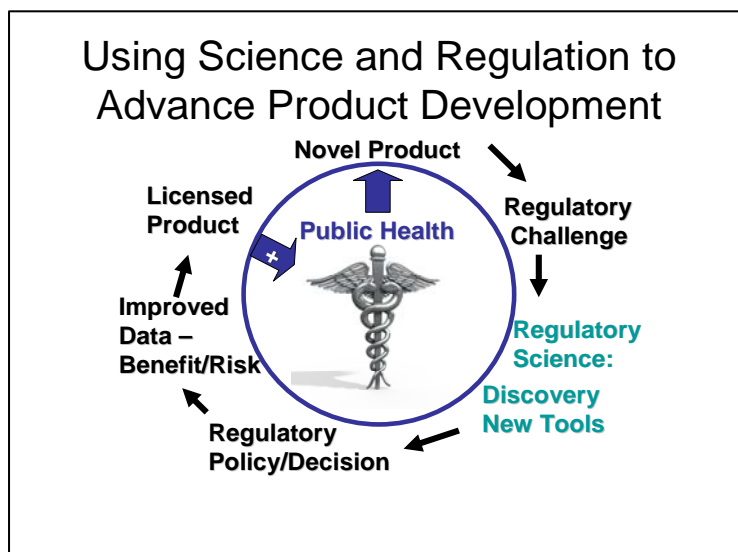


Figure 3. Using Science and Regulation to Advance Product Development.

CBER STRATEGIC PLAN FOR REGULATORY SCIENCE AND RESEARCH

The center ADR developed the strategic plan under the direction of the Center Director. The purpose of the plan is to explain the vision and provide the long term strategic goals, objectives, and strategies for implementation for regulatory science and research over the next four years.

CBER Vision for Regulatory Science and Research

CBER's scientific research will be proactive, anticipating regulatory and public health issues while being responsive to emerging public health and regulatory issues. Therefore, our research will be collaborative, of highest quality and relevance, and integral to the center's regulatory mission and public health portfolio. The research program will provide CBER with appropriate scientific expertise, tools, and data to support science-based decision-making and policy development.

Regulatory Science and Research Priorities

The aim of our scientific research is to ensure the safety, efficacy, and availability of biological products and to ensure the development of appropriate regulatory pathways. The specific priorities will be discussed under each strategic goal.

The Regulatory Science and Research Strategic Goals are based on the CBER strategic goals. Included in this strategic plan is a cross-cutting goal focused on

research excellence and accountability. For each strategic goal, the plan summarizes how we will direct regulatory science and research priorities to specific areas. Each area includes a general description of activity, strategies for implementation, and an outcome statement.

The five strategic goals for regulatory science and research are to:

1. **Increase** the nation's preparedness to address threats as a result of terrorism and pandemic influenza and emerging infectious diseases
2. **Improve** global public health through international collaboration including research and information sharing
3. **Enhance** the ability of advanced science and technology to facilitate development of safe and effective biological products
4. **Ensure** the safety of biological products
5. **Enhance** research excellence and accountability

Regulatory Science and Research Strategic Goals

I. Increase the nation's preparedness to address threats as a result of terrorism and pandemic influenza and emerging infectious diseases.

CBER regulatory science and research priorities will focus on developing a comprehensive approach to rapid pathogen detection, enhancing preparedness for seasonal and influenza vaccines, and facilitating licensure of medical countermeasures for treating or preventing diseases due to bioterrorist attacks.

A. Rapid Pathogen Detection

The threat posed by transmissible infectious microorganisms in biological products has led to the establishment of a variety of safety measures: donors of blood and tissues must be tested for pathogens and deferred if necessary; biologic products must be tested for bacteria and fungi during manufacture whenever feasible; and vaccines, cell and gene therapies, and the cell substrates used to manufacture these products must be tested for a wide variety of infectious agents that are not amendable to methods for inactivating or removing them during manufacture. Furthermore, newly emerging infectious agents could also threaten the safety of blood and tissues due to the spread of disease vectors (e.g., dengue), travel and immigration (e.g., malaria), terrorism (e.g., anthrax), or previously rare or unknown agents.

Strategies for Implementation

CBER will support a proactive, comprehensive approach to pathogen detection and reduction, responding to new and emerging safety threats by:

- Working collaboratively within the center and with sister agencies in DHHS to identify, assess, monitor and prioritize emerging threats
- Creating a scientific team to facilitate development and availability of reagents, samples and methods for developing, validating, and deploying screening tests for emerging priority pathogens through public-private collaboration

- Assessing and encouraging development of new technologies that enable rapid, sensitive, specific, high throughput, cost-effective screening of blood, tissues and their donors, and other biologics for known, emerging and unknown pathogens, including monitoring and testing during manufacturing
- Developing and evaluating methods for broad pathogen detection
- Assessing, developing, and improving new methods to inactivate pathogens without impairing product function
- Improving microbial safety of human tissue products by developing and evaluating better processing conditions, pathogen inactivation, and/or pathogen detection

Outcome:

CBER will enhance the safety of blood and tissue supplies through improved methods and implementation procedures for detecting or inactivating pathogens.

B. Preparedness for Pandemic Influenza

CBER ensures the safety, quality, and potency of both seasonal and pandemic influenza vaccines.

Strategies for Implementation

CBER will prepare for pandemic influenza while enhancing yearly review for seasonal influenza vaccines by:

- Developing and evaluating improved tools and methods to enhance safety, effectiveness, quality, and potency testing of influenza vaccines, including faster methods to develop reference reagents and to perform tests for potency and sterility to allow for more rapid response in pandemics
- Identifying and implementing new approaches to reliably generate seed stocks that replicate more efficiently, thus speeding vaccine manufacture
- Developing and evaluating preclinical methods to screen novel adjuvants for adverse effects prior to clinical trials, thus increasing the availability of highly effective vaccines during a pandemic
- Evaluating the safety of new production methods for influenza vaccines, such as use of mammalian cell substrates

Outcome:

CBER will achieve more rapid preparation, testing, and deployment of seasonal and pandemic influenza vaccines that are safe, potent, and effective.

C. Preparedness for Biological, Chemical or Radiologic Acts of Terrorism

CBER focuses on vaccines and therapeutics to prevent or treat diseases caused by bioterrorism agents and on regenerative medicine products for the treatment of victims of chemical or radiological terrorist attacks.

1. Bioterrorism Agents

The inability to conduct human efficacy studies because such studies are not ethical or feasible means that the development of most vaccines and therapeutics for bioterrorism agents will be based on nonclinical data, where possible.³

Strategies for Implementation

CBER will facilitate use of the Animal Rule to support licensure of products for treating or preventing bioterrorist attacks by:

- Developing and evaluating nonclinical models to study pathogenesis and identify relevant correlates of immunity
- Creating methods and models to study potential toxic effects of vaccine antigens, adjuvants, and other components of vaccines
- Determining biomarkers of pathogenicity and developing new methods to evaluate and ensure the safety of live vaccines
- Studying mechanisms of vaccine-related adverse events, ways to mitigate them, and biomarkers of predisposition to adverse events
- Creating methods to evaluate and improve immunogenicity, potency, and efficacy of vaccines
- Studying innate and adaptive immunity against viral and bacterial diseases, and mechanisms of immunopathology (including allergy), and developing new approaches to inducing protective immunity

Outcome:

CBER will contribute to development and availability of new methods and models to assess medical countermeasures for treating or preventing bioterrorist attacks.

2. Chemical or Radiological Agents

CBER regulates products used to treat persons injured by chemical or radiological acts of terrorism. These products include cell-based therapies for wound repair, tissue regeneration, and reconstitution of bone marrow.

Strategies for Implementation

CBER will prepare to evaluate novel regenerative medicine products for treating victims of chemical or radiological terrorist attacks by:

- Improving the safety and efficacy of stem cell-based products and combination and tissue engineering medical products by using systems biology, modern methods of cell characterization (e.g., genomics, epigenetic analysis, proteomics, cell surface phenotypic analysis, and measures of in vitro function), and assessment and development of animal models to identify biomarkers for appropriate cell differentiation state and function, localization, and controlled proliferation.

³ For more on requirements for licensure under these conditions see ["The Animal Rule": New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible; Final Rule, 5/31/2002.](#)

Outcome:

CBER will increase the availability of safe and effective medical countermeasures to prevent or treat conditions caused by biological, chemical or radiologic terrorist attacks.

II. *Improve global public health through international collaboration including research and information sharing.*

CBER regulatory science and research priorities will focus on working with international partners and developing countries in vaccines related projects and overseeing the screening of the blood supply for infectious agents in an effort to reduce the spread of global infectious disease.

Strategies for Implementation

CBER research will address public health and regulatory problems of global significance by:

- Developing and evaluating pre-clinical models to study pathogenesis and protective immunity and to identify correlates of immunity that facilitate development of vaccines for the developing world (e.g., TB, malaria, yellow fever, dengue)
- Implementing international collaborations for surveillance of new forms of HIV that evade blood screening assays by evaluating HIV strains in Africa and elsewhere around the world
- Developing panels, reagents, and methods to detect emerging threats to the blood supply (e.g., babesia, malaria, dengue virus, and chikungunya virus)
- Collaborating with the World Health Organization, government agencies or private foundations to support and enhance our research into under-funded global health diseases
- Transferring FDA advances to the public domain to improve efficacy and safety of vaccines and blood and blood products that promote global public health

Outcome:

CBER will improve the availability of safe and effective medical products to address global public health problems.

III. *Enhance the ability of advanced science and technology to facilitate development of safe and effective biological products.*

CBER regulatory science and research priorities will focus on improving CBER scientists need to keep pace with, evaluate, and implement when applicable, innovative technologies to improve test methods for both currently licensed products and those under development. The aim is to identify ways that advanced science and technology can enhance safety, quality, potency, or availability of CBER-regulated biological products.

In addition, CBER must maintain and enhance its scientific expertise, infrastructure, and internal processes in order to efficiently regulate innovative products now being developed to treat chronic diseases such as cancer, and rare disorders. This preparation will also be key to CBER's ability to perform in-house research that addresses potential scientific challenges to product development due

to lack of such critical tools as appropriate test methods, preclinical models, and clinical biomarkers.

A. Evaluate and implement novel methods and technology

CBER will evaluate and implement novel methods to improve reliability, sensitivity, and specificity of assays for product development and lot release.

Strategies for Implementation:

CBER will evaluate and implement novel methods based on recent technologic developments that will enhance product safety or quality by:

- Developing highly sensitive, rapid methods to test the sterility of biological products
- Evaluating the utility of novel scientific technologies such as NMR, genomics, and epigenomics for product characterization, leading to improved consistency and reliability of manufacturing processes for complex biological products under development or already licensed
- Evaluating and developing methods for characterizing recombinant proteins to improve consistency, safety, and quality and facilitate licensure of biosimilars
- Evaluating the safety and efficacy of nanomaterials used in medical products
- Performing statistical research to support development and evaluation of new bioassays and tests

Outcome:

CBER will achieve timely application of novel methods and technology to improve product safety, quality, and availability.

B. Facilitate development of safe, effective, and innovative products for regenerative medicine and to treat chronic diseases such as cancer, and rare diseases

CBER will facilitate development of innovative products for unmet medical needs, such as regenerative medicine as well as novel treatments of cancer and chronic and rare diseases, by:

- Developing improved tools for clinical trial design and analysis
- Implementing multi-disciplinary research to improve our understanding of how to regulate cell-based therapies such as stem cell-derived products and tissue engineered medical products
- Performing research into nonclinical models and methods to assess safety and potency of products for therapy of cancer and rare diseases

1. Clinical Trial Design and Analysis Facilitating New Product Development

CBER will help bring innovative products to the market more quickly and efficiently by using and developing statistical methods for clinical trial design and analysis, including simulation modeling, Bayesian and adaptive designs, and other analytic approaches to improve evaluation of product safety and efficacy.

Strategies for Implementation:

CBER will implement the use of novel approaches to clinical trial design and analysis by:

- Developing mathematical and statistical models to design and simulate the processes and factors comprising a clinical trial
- Improving collaborative and training opportunities for staff in adaptive/flexible design and Bayesian statistical methods to facilitate appropriate use of these tools during clinical development of innovative therapies

Outcome:

CBER will advance innovative products to the marketplace more quickly, efficiently, and economically.

2. Innovative Products Relying on Living Cells

Regenerative medicine is an emerging multi-disciplinary field whose products hold great potential for treating or curing genetic disorders, neurological conditions, diabetes, arthritis, cancer and other diseases, by repairing damaged tissues and ultimately, producing artificial organs for transplantation.

A key strategy in this field is the use of human stem cells to produce cells that have the specific structure and function needed to treat disease, replace failed organs and tissues, or restore their function. CBER must learn how to assess the risks of these novel technologies and identify product characteristics that can predict safety and efficacy in quality-control tests. These characteristics will be critical for predicting if a specific stem-cell-derived product will perform the desired function, or alternatively migrate to an incorrect location, form a tumor, or have unstable function or structural features after implantation. Assessing these characteristics is complicated by the lack of relevant and predictive *in vitro* and animal models.

CBER also regulates tissue-engineered medical products (TEMPs), which often are combination products comprised of two or more regulated components (i.e., biologic/device, biologic/drug, biologic/device/drug). As a result, the components of a combination product may have been developed with disparate manufacturing techniques and controls that CBER must take into account during the regulatory process. Furthermore, interactions among components during product maturation *in vitro* or *in vivo* (e.g. cell-scaffold constructs) and the potential for changes in product quality during clinical use (e.g., advanced cell delivery systems) introduce additional regulatory concerns. CBER seeks to characterize parameters that predict product safety and efficacy but that are not excessively burdensome, in order to facilitate development of safe and effective TEMPs.

Strategies for Implementation

CBER will facilitate development of safe and effective cellular therapeutics for treating human disease and:

- Identifying critical in vitro and in vivo markers of product safety, quality, and potency, especially characteristics of cell therapy products that are measurable in vitro and correlate with in vivo outcomes
- Developing animal models to evaluate stem-cell-derived and other cell therapies and tissue-engineered products, and using state-of-the-art imaging techniques to observe cell fate, migration, and function, in animal models
- Enhancing expertise in stem cell biology, differentiation pathways, impact of interactions between living cells and materials, and various forms of encapsulation likely to be used in tissue engineered products
- Developing Cross-Agency efforts to address the challenges posed by novel combination products for regenerative medicine.

Outcome:

CBER will achieve more rapid development of safe and effective therapies for regenerative medicine, chronic diseases such as cancer, and rare disorders, based on living cells, including stem cell-derived and tissue engineered medical products.

3. Innovative Products for Treating Cancer, including Cell and Gene Therapy, Tumor Vaccines, and Immunotherapy

CBER has regulatory oversight of novel cancer treatments, such as cell and gene therapies, and tumor vaccines and other immunotherapy products. Although some products are in phase 3 clinical trials (last phase of investigational testing prior to submitting biologics license application), nearing license application, or already licensed, many fail during phase 3 trials. In addition, some products have been associated with unforeseen adverse events, lack of activity, or inconsistent product performance, despite satisfying current lot release and preclinical testing requirements. CBER regulators and industry need new test methods and biomarkers that can predict safety and effective clinical performance and thus help avoid the loss of time and money caused by late stage product failures.

Strategies for Implementation:

CBER will facilitate development of novel therapeutic approaches to treat cancer by:

- Supporting virology, molecular biology, tumor biology, and immunology studies of the safety and efficacy of gene transfer and tumor vaccines
- Developing and analyzing animal models for their reliability and sensitivity in detecting potential adverse events associated with gene transfer, tumor vaccines and immunotherapy products
- Developing and analyzing animal models for cancer to assess safety and efficacy of tumor therapies

Outcome:

CBER will contribute to more timely availability of innovative, safe, and effective therapies for cancer patients.

4. Novel therapies for rare diseases.

In the United States, approximately 1 of every 5,000 individuals has a "rare disease," that is, a disease that affects less than 200,000 individuals (e.g.,

hemophilia, cystic fibrosis, and many even rarer conditions, including some forms of blindness or immune deficiency). Many treatments are only palliative and not curative. Therefore, there is a need for improved treatments that cure rare inherited diseases, such as by recombinant proteins or gene therapy.

Strategies for Implementation:

CBER will facilitate development of novel therapies for rare diseases by:

- Developing and evaluating improved preclinical models to assess safety and efficacy of recombinant protein and gene therapies
- Developing and assessing new ways to transfer genes that improve safety and efficacy of gene therapy
- Evaluating and developing new ways to improve recombinant protein characterization to improve product quality and facilitate licensure of biosimilars

Outcome:

CBER will make safe and effective novel therapies for rare diseases more readily available.

IV. Ensure the safety of biological products.

CBER regulatory science and research priorities will focus on developing improved surveillance of adverse events that may be caused by investigational products that may occur very infrequently during clinical trials, when relatively few individuals are treated with them.

Therefore, it is critical to conduct surveillance for possible adverse events after the product comes to market, when significantly more people are exposed, and if possible, to identify individual risk factors that predispose individuals to specific adverse events. In the future, personalized medicine may help ensure patients receive the correct product at the correct dose, and avoid products which would be particularly risky for them, thus improving risk-benefit ratio of treatments.

Strategies for Implementation

CBER will enhance its ability to detect low frequency adverse events associated with licensed products by:

- Partnering with government agencies and private organizations to access large healthcare datasets that enable more rapid and sensitive detection and study of adverse events caused by biologics (e.g., through initiatives such as the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program and the Blood Safety Continuous Active-surveillance Network (BloodSCAN) under the FDA's Mini-Sentinel initiative.
- Developing and implementing methods to monitor and analyze a broad range of potential biologics-related adverse events
- Developing and assessing methods for safety signal detection and developing protocols and thresholds for confirmatory studies
- Conducting quantitative risk assessments and risk-benefit assessments to assess the impact of external events and influences on the safety and/or availability of biologics (e.g., the impact of pandemic influenza on blood supply)

- Enhancing in-house human genomics expertise and partnering with other government agencies to facilitate evaluation of regulatory genomics data for regulatory decision-making
- Partnering with government and private sectors in pre- and post-approval studies to obtain and analyze human genomic data to determine the significance of genetic associations with specific adverse events to obtain a better understanding of the etiology of adverse effects from biologic products to facilitate the development of personalized medicine

Outcome:

CBER may improve the safety of biological products by using faster and more sensitive methods for adverse event surveillance and support the adoption of personalized medicine.

V. Enhance research excellence and accountability

CBER regulatory science and research priorities will focus on enhancing its regulatory science and research priorities by improving its laboratories, scientific computing capabilities, and scientific skill sets. We will also provide additional human resource capabilities. As part of this effort we will strengthen our evaluation processes and evaluate CBER regulatory science and research programs periodically for regulatory and public health relevance, productivity, and quality.

A. Establish an infrastructure that supports high-quality state-of-the-art scientific investigations.

Consolidating laboratory and office staff at the White Oak campus will enable CBER scientists to work in a state-of-the-art research facility that supports current and future research programs. This facility will include computer-intensive scientific technologies that are critical for addressing important regulatory and public health issues. Indeed, recent developments in high performance hardware and software have made unprecedented computer resources available to CBER researchers, which the center will use for: molecular modeling (e.g., vaccine safety studies), microarray and genomics (e.g., improved characterization of cell therapies, vaccines and blood products), proteomics and metabolomics (e.g., improved vaccine characterization and blood product safety), systems biology (e.g., improved characterization of cells and increased tissue safety), post-marketing surveillance of large databases (e.g., monitoring the safety of biologics through their life cycle), simulation and Monte Carlo modeling (e.g., safety decision analysis support), clinical trials and Bayesian analyses (e.g., making marketed biologics safer).

Strategies for Implementation:

CBER will design the laboratory building at the White Oak campus with expanded capacity in the vivarium, the biotechnology core facility, BSL-3 dedicated suites, NMR suite, and storage areas by:

- Expanding imaging capacity (7.0 Tesla small animal magnetic resonance imaging (MRI), digital X-ray, In vivo Imaging System (IVIS), ultrasound, and transmission electron microscope) for sophisticated studies of products, allowing in-life measurements and improved preclinical assessment of biologics

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- Supplementing core facility with additional technologic capabilities to support high throughput sequencing (“next generation”), flow cytometry (sterile sorting and multi-colorimetric flow cytometric analysis), and high resolution confocal microscopy (for living and fixed cells, tissues, and whole animals)
- Establishing ten Biological Safety Level (BSL)-3 suites to enable work with at least 12 infectious agents, accommodating 36 principal investigators; capacity for animal holding rooms and capability for sterile sorting and live cell imaging of infected cells by state-of-the-art flow cytometry and confocal microscopy within BSL-3 suites
- Providing a suite to support nuclear magnetic resonance equipment (NMR), with plans to replace current NMRs with models having larger magnets as they become available and are needed for studies requiring improved molecular resolution.

CBER will oversee execution of the design of the new laboratory by:

- Monitoring the construction phase of the laboratory building
- Providing scientific equipment by transfer from the previous buildings, procurement when replacement is necessary, and installation of scientific equipment by qualified personnel
- Resourcing and planning for optimal maintenance and operation of the new facility and scientific equipment

CBER will meet the ongoing and future scientific and computing resource needs of our research programs by developing collaborative approaches to facilitate:

- Seeking outside funding from private foundations or government agencies with shared goals
- Protecting intellectual property arising from discoveries within CBER laboratories
- Implementing CRADAs, Research Collaboration Agreements, and Material Transfer Agreements that facilitate scientific collaborations with scientists in other FDA Centers, NIH, other government agencies, international organizations, academia, or private industry, thus leveraging our scientific expertise and resources
- Identifying and utilizing high performance computing resources, as proposed in the CBER high performance computing strategic road map
- Developing improved and secure data storage and network access and bandwidth
- Improving FDA processes for procuring and accessing scientific computing software & hardware
- Improving availability of application engineering expertise and support for advanced computing
- Leveraging use of and access to high performance computing resources among other FDA centers and NIH

Outcome:

CBER will make available state-of-the-art laboratory facilities and scientific computing resources to support the ability of CBER scientists to evaluate and use novel technologies in assessing innovative medical products, and solve regulatory issues with an impact on the development of complex biological products.

B. Training and leveraging resources

CBER must maintain, update, and enhance the scientific expertise of staff in order to address novel regulatory issues through scientific research. Therefore, the center must provide resources to ensure that the scientific staff can evaluate and use state-of-the-art technology and remain current in their scientific knowledge. CBER will achieve this by combining training opportunities and support for collaborative science.

Strategies for Implementation:

CBER will provide training opportunities that include:

- Attendance at relevant scientific meetings and specific technical or scientific courses to update expertise or skills
- Providing CBER training courses to support and strengthen core skills for scientific research (e.g., grant application and manuscript writing)
- Supporting short sabbaticals to collaborating laboratories for training in new technologies or methods that will enhance the center's own research program

CBER will leverage resources and human capital opportunities to solve regulatory issues with an impact on development of complex biological products by:

- Identifying and applying funding from private foundations or government agencies with shared goals
- Protecting intellectual property arising from discoveries made in CBER laboratories
- Implementing CRADAs, Research Collaboration Agreements, and Material Transfer Agreements that facilitate scientific collaborations with scientists in other FDA Centers, NIH, other government agencies, international organizations, academia, or private industry, thus leveraging our scientific expertise and resources
- Using fellowship programs (e.g., ORISE, Service and Commissioner's Fellowship Programs, NCI-DA Inter-Agency Oncology Task Force) to attract talented scientists with skills and knowledge needed at CBER and provide them scientific training

Outcome:

CBER will recruit and retain scientific staff with up-to-date skills and knowledge that enables them to perform research that utilizes innovative science and technology.

C. Evaluation of research programs to ensure quality, productivity, and FDA mission relevance

CBER will strengthen its evaluation processes by ensuring CBER regulatory science and research programs are evaluated periodically for regulatory and public health relevance, productivity, and quality.

Strategies for Implementation:

CBER will support and perform research relevant to public health and regulatory priorities in an efficient and scientifically rigorous manner; we will continue to implement the following research management strategies:

- Ensuring the most relevant regulatory problems are addressed by co-sponsoring and participating in workshops, participating in advisory committee meetings, attending relevant scientific and regulatory meetings, and engaging outside experts to review our scientific programs on a regular basis
- Engaging in internal discussions to identify emerging scientific and regulatory issues that can be effectively addressed by CBER's research and use those discussions as the basis of office- and center-wide research priorities
- Using peer review and managerial oversight to allocate resources to highly qualified, productive principal investigators doing rigorous science relevant to stated priorities
- Using internal peer review to evaluate scientific relevance, quality, and productivity every four years, or when a scientist is deemed ready for conversion to a permanent position or promotion
- Using formal external scientific peer review of principal investigators through site visits every four years to evaluate the public health and regulatory impact, quality, and productivity of their scientific programs
- Using annual reporting via an online database of scientific accomplishments, future plans, publications of peer-reviewed scientific articles, relevant guidance documents, and other relevant output to annually evaluate the outcomes of CBER research programs
- Allocating research resources to scientific programs that address CBER's long-term objectives, stated regulatory science and research priorities, and represent high quality well-designed, productive science, based on the above-mentioned management strategies

Outcome:

CBER will perform high-quality, productive research that addresses critical regulatory and public health scientific problems and that supports regulatory decision-making and policy development.

Appendix A – CBER’s Support of FDA Research Initiatives

FDA’s Advancing Regulatory Science Initiative

In August, 2011, FDA issued a Strategic Plan, “Advancing Regulatory Science at FDA” (available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm>). This cross-cutting strategic plan provides a guide to implement FDA’s commitment to advancing regulatory science and innovation made in the FDA’s Strategic Priorities documents issued in April 2011. The FDA Strategic Priorities document defines “Regulatory Science” as the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.

The Strategic Plan identifies eight priority areas for regulatory science that would support FDA’s public health and regulatory mission:

- 1) Modernize toxicology to enhance product safety
- 2) Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes
- 3) Support new approaches to improve product manufacturing and quality
- 4) Ensure FDA readiness to evaluate innovative emerging technologies
- 5) Harness diverse data through information sciences to improve health outcomes
- 6) Implement a new prevention-focused food safety system to protect public health
- 7) Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security
- 8) Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products

Building on commitments in the FDA’s Strategic Plan and in CBER’s Strategic Plan, CBER has developed a Strategic Plan for Regulatory Science and Research that outlines its goals, objectives and strategies for supporting the priority areas (except for the food safety-related area) of regulatory science supporting the health of the American public and global public health.

In addition, this plan supports FDA-wide initiatives that have a regulatory science component built into them. These initiatives are: 1) Nanotechnology Regulatory Science Initiative; and 2) Medical Countermeasures Initiative. A brief description and CBER’s contributions to each of these initiatives are provided.

Regulatory Science and Innovation (formerly Critical Path Initiative)

FDA launched Critical Path Initiative (CPI) in 2006 to overcome product development roadblocks using existing and newly created scientific knowledge, new methodology and tools, and nonclinical models. The goals of CPI include:

- 1) Improving drug evaluation tools
- 2) Streamlining clinical trials
- 3) Harnessing the power of bioinformatics
- 4) Advancing manufacturing technologies using 21st Century science
- 5) Developing innovative solutions to urgent public health needs

The CPI was later expanded in scope to include all FDA-regulated products. The Office of the Chief Scientists (OCS) administers the CPI through its Office of Regulatory Science and Innovation. This organization provides central coordination for the CPI; leads certain FDA-wide CPI projects, and supports CPI projects in the centers with funding, staffing, and/or project management.

FDA's Nanotechnology Regulatory Science Initiative

The FDA Nanotechnology program includes support in regulatory science intended to achieve three objectives:

- 1) Increased training for FDA staff to support review activities of FDA-regulated products that contain engineered nanomaterials or use nanotechnology for the manufacturing process
- 2) Creation of two core laboratories that provide equipment and methodologies to allow FDA scientists to further their research to support development of safe and effective FDA-regulated products
- 3) Establishment of a competitive FDA-wide grants program, called Collaborative Opportunities for Research Excellence in Science. (Details about these three areas and the implementation plan for the FDA's Nanotechnology Regulatory Science Initiative are available at <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm>)

CBER participates in the Nanotechnology Regulatory Science Initiative by serving on the Nanotechnology Task Force, a cross-FDA body that oversees this initiative, and through targeted research relevant to CBER-regulated nanotechnology products.

FDA's Medical Countermeasures Initiative

The FDA's Medical Countermeasures initiative (or MCMi) was developed in order to facilitate development of novel medical countermeasures used in response to natural or man-made public health disasters. The MCMi is a critical component to the Nation's preparedness efforts. Natural public health disasters include a novel strain of influenza that could cause a pandemic or other emerging infectious diseases. Man-made disasters arising from potential terrorist attacks include bioterrorist, chemical, burn, blast, or nuclear attacks. The MCMi has three pillars:

- 1) Enhancing the regulatory review process for the highest priority medical countermeasures and related technologies
- 2) Advancing regulatory science for medical countermeasure development
- 3) Optimizing our regulatory and legal framework

CBER will continue to use its scientific resources to address regulatory science needs to support development of MCMs, including those related to preparedness for pandemic influenza, emerging infectious disease, and bioterrorist threat agents.

Appendix B – CBER Organization

