Food and Drug Administration (FDA) Science Board Subcommittee Review of the Center for Biologics Evaluation and Research (CBER) Research Programs

2017

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Charge to the Science Board (Note: Formal, full charge, found in Appendix 3)

Briefly, the charge to the Science Board subcommittee is to address:

1) How CBER's scientific endeavors support the Center's regulatory mission.

2) Recommended changes in CBER to its regulatory science research portfolio to best accomplish our regulatory and public health mission.

3) Gaps in regulatory science capabilities or expertise.

4) Opportunities for collaboration to better leverage CBER's regulatory science programs.

Executive Summary

The Center for Biologics Evaluation and Research (CBER) has maintained and advanced a strong research program that effectively supports its regulatory and public health mission. The researcher-reviewer model utilized by CBER has proven to be an extraordinarily effective approach, one that provides flexibility to recruit and retain highly qualified scientists. In addition, CBER engages in a number of external research collaborations that are not only essential to maintain active regulatory science research programs, but also help CBER be well-positioned to anticipate and respond to emerging regulatory challenges. CBER also provides critical core facilities to support research initiatives across CBER, and in some cases other parts of FDA. In general, CBER has been responsive to addressing emerging regulatory challenges, in particular, pandemic and other infectious disease threats to the public health.

Major recommendations:

CBER should develop a Center-wide horizon-scanning process that identifies gaps to inform development of research priorities and planning. This plan should assure that strategic and budget planning reflect appropriate distribution of resources weighted toward emerging and rapidly evolving arenas.

To augment CBER's ability to respond rapidly to emerging threats and rapid technology developments, CBER should engage the Regulatory Science Council and the Resource Committee to develop contingency plans to allow rapid shifting of resources, projects, and personnel with less disruption.

External collaborations should be expanded to include personnel exchanges with other government agencies such as National Institutes of Health (NIH), Center for Disease Control (CDC), Department of Defense (DoD), etc, as well as through Public Private Partnership activities, particularly in emerging scientific areas of regulatory significance.

To support the researcher-reviewer model, enhance ability to recruit and retain scientific talent in key emerging science and technology, CBER should consider the following:

Designating some amount of "protected time" for research activities;
Consider a sabbatical program for intramural scientists in academic laboratories
Assure appropriate travel funding for investigators to stay abreast of emerging technologies.

Expand mentorship/professional development program for staff.

Steps should be taken to expand and diversify training programs to recruit talented post-baccalaureate and post-doctoral scientists to the agency.

CBER core facilities are an important resource and providing necessary resources and staff should be a priority.

Introduction

By virtue of the designation as a center for evaluation and research, CBER has a key responsibility to conduct research. The mission to conduct research enhances the overall mission of the FDA to provide safe and effective drugs, veterinary medicines, food, biological products and medical devices. A large proportion of time and effort is allocated to the evaluation of new products, but research is necessary to advance regulatory decision-making and to maintain the expertise needed to adequately evaluate these products. CBER embraces the researcher-reviewer model where a subset of reviewers are tasked with spending some of their time on research.

CBER oversees a wide variety of products including vaccines, certain recombinant proteins, cell and gene therapies, tissues, and blood and blood components. Each of these product areas has a separate office, for example, the Office of Vaccines Research and Review focuses on vaccines. In addition, there is a cross-cutting Office of Biostatistics and Epidemiology that supports all the product areas.

This report is organized into five parts. The first part provides the key findings and recommendations that are cross-cutting and relevant to the entire CBER research program. The next four parts are specific to each of the four Offices that perform research as a portion of their overall responsibilities: Office of Biostatistics and Epidemiology, Office of Blood Research and Review, Office of Tissues and Advanced Therapies, and Office of Vaccines Research and Review.

CBER Cross-Cutting Themes

GENERAL OVERVIEW AND RECOMMENDATIONS

The Subcommittee agreed that CBER has been very effective in conducting its regulatory and public health mission, particularly in maintaining and in some areas advancing a strong research program despite growing budgetary constraints, evolving demands and repositioning of resources. Additionally, the new management process recently implemented by CBER should further support their program. These accomplishments are substantial. Nonetheless, the Subcommittee, according to its charge, identified several areas that CBER should consider addressing to improve their ability to anticipate future regulatory challenges and respond to internal and external demands. There are several cross-cutting issues critical to CBER's research, training, and core scientific infrastructure to support its broad regulatory and public health missions.

SETTING RESEARCH PRIORITIES AND PROVIDING A NIMBLE SCIENTIFIC INFRASTRUCTURE

Key Findings

CBER has recognized the importance of ensuring the Center is prepared to anticipate emerging biological products and this is reflected as a key consideration in their interim strategic plan, particularly through Goal 4 (Preparing for future regulatory and public health challenges).

While CBER has made hiring decisions to address specific scientific gaps, the broader Center-wide process for prioritizing intramural research areas and conducting horizon scanning is uncertain. The current approach appears primarily driven at the branch and office level, but it is unclear how this is informed by or tied to broader CBER-wide horizon scanning and needs assessments.

Given the broad responsibilities and corresponding science portfolio for CBER, defining gaps and setting overarching scientific priorities seems critical. At the same time, ensuring preparedness and response to domestic and global public health needs and emergencies creates additional demands on FDA, in some cases requiring rapid redeployment of existing resources and scientific programs to address emerging needs. These emergency responses may on occasion leave some programs understaffed for potentially long periods.

The CBER scientific program has many strengths, yet uncertainties in the federal budget make planning for future growth difficult. Additionally, it is difficult to expand programs at a time when other traditional funding sources are similarly stretched for research support. It is imperative that each program be integrated across CBER to maximize the contribution of each laboratory to their Office and the overall mission of CBER.

Recommendations

CBER should consider a broader horizon scanning process that would then help identify scientific gaps and recommend research priorities across the Center. This process should result in developing a center-wide plan that outlines approaches for a combination of both intramural programs and extramural collaborations to address these needs. The intramural component would provide broad goals and a general framework or outline for how each of the offices would contribute to addressing these needs, while the offices could then develop the more specific implementation plan at the office and laboratory level based on their expertise and capabilities. The plan should maintain a level of flexibility and independence to the offices and laboratories and, at the same time, maintain a clear alignment with a broader strategic research plan. This overarching plan and corresponding alignment with extramural initiatives and intramural offices and labs would also provide for a future evaluation of progress on these research priorities. Given the Charter for the CBER Regulatory Science Council (RSC), this group would appear to be the appropriate one to lead this activity for the Center.

Integrated with this planning process is the need to even further ensure nimble responses to future needs and enhance the capacity to shift resources and projects more rapidly to respond to immediate requirements and emergencies. While CBER has been very effective in supporting responses to bioterrorism threats and emerging infectious diseases, these situations and rapid technology developments will continue to arise at an even faster rate. Additionally, this will likely occur in a climate of increased funding constraints. Creating an even more nimble and adaptive governance structure and culture will be essential for CBER, and the RSC and CBER Resource Committee should develop contingency plans to provide the ability to shift resources and projects (with personnel) in a more rapid and less disruptive manner. This will be tied to a more transparent strategic research plan with a mix of intramural programs and extramural research collaborations, including an effort to identify additional opportunities for external funding to support individual and collaborative research projects.

RESEARCH COLLABORATIONS

Key Findings

CBER engages in several FDA-wide and external research collaborations, particularly with academic institutions, industry (via Research Collaboration Agreement and Cooperative Research and Development Agreements) and other government agencies, that are not only essential to maintain active regulatory science research programs, but also help CBER to be well positioned to anticipate and respond to emerging regulatory challenges.

Recommendations

There would be value in further expanding collaborations and personnel exchanges with agencies addressing similar emerging areas, as the recent responses to Ebola and Zika have demonstrated. Key research partners could include NIH, CDC, and DoD, who have shared research challenges and gaps where a scientific collaboration is well suited.

Additional incentives should be provided for these external collaborations, including reviewing opportunities and any barriers for individually (or jointly) applying for funding opportunities to support these collaborations. Identifying external funding sources to support these collaborations was identified as a challenge and approaches utilizing agency contracts and interagency transfers should be explored. {Note: specific external collaborations would also be informed by the horizon scanning and research planning process outlined above}

The Subcommittee believes CBER would also benefit from having increased knowledge of what is coming in the pre-Investigational New Drug (IND) pipeline, not only from large pharma and smaller biotech companies but also from earlier stage discovery research transitioning from University labs. CBER participates in some of the existing consortia and Public Private Partnership activities through groups such as the Foundation for NIH and the Critical Path Institute, and sponsors scientific workshops relevant to emerging product areas. However, increased engagement in relevant groups, and perhaps sponsoring additional workshops that particularly engage the private sector on emerging scientific areas, should be considered.

While CBER participates in many internal collaborations with other FDA Centers, the subcommittee suggests that these collaborative efforts could be expanded and further utilized as a valuable resource for research and training.

RESEARCHER-REVIEWER MODEL

Key Findings

The Researcher-Reviewer Model utilized by CBER has proved to be an extraordinarily effective approach, one that provides flexibility to recruit and retain scientists in key areas of need. Indeed, this model has been recommended to other FDA centers. The Researcher-Reviewer role also serves as a critical hybrid model for CBER to support diverse missions and anticipate emerging regulatory science. This allows individuals to maintain their research activities and scientific expertise, which then further informs their ability to optimally carry out their regulatory responsibilities. At the same time, these diverse responsibilities can create significant challenges when other pressing regulatory demands, emergency responses or other priorities emerge.

Recommendations

The Researcher-Reviewer role is central to CBER's meeting its scientific, regulatory and broad public health responsibilities and should be strongly supported to ensure that there are sufficient incentives and flexibility to maintain this role. Because the researcher-reviewer models serve as a cornerstone of CBER's regulatory science effort, consideration should be given to designating some amount of "protected time" for these research activities.

Given the diverse responsibilities and challenges with the workload for Researcher-Reviewers, one of the first areas to be adversely affected by competing priorities is likely to be the scientific duties: research, meetings/conferences, peer review, etc. Flexibility and increased incentives to maintain this scientific expertise is critical.

TRAINING, PROFESSIONAL DEVELOPMENT AND FUTURE WORKFORCE

Key Findings

Supporting training and professional development opportunities for current CBER staff is an important element to maintaining awareness of emerging science and anticipating future biological products that the agency will need to address. In addition to more formal course work, this can include participating in meetings and conferences and engaging in peer review. Having current staff participate in details/exchanges to other agencies or academia can also provide unique opportunities for further scientific and professional development, bringing that experience and knowledge back to the agency when they return.

In addition to FDA personnel participating in exchanges, bilateral exchanges with other agencies and academia can also contribute to bringing new scientific expertise into the agency, and in some cases help encourage future external research collaborations or recruiting future employees to the agency.

To initially recruit a range of scientists and other professions to the FDA, CBER regularly utilizes the Oak Ridge Institute for Science Education (ORISE) Fellowship and other fellowship programs to bring in post- baccalaureate and postdoctoral fellows, as well as bringing in staff fellows and senior staff fellows in temporary government roles. The broader need to address any challenges with utilizing the ORISE Fellow mechanism and recommendations for other programs has been raised in prior reports from the Science Board (*see* Scientific Engagement report). In addition, continued investment and streamlining of the fellow/postdoc program will not only assure stability to the critical research programs, but will also serve to engage talent for future FDA staff positions.

Recommendations

To further stay apprised of emerging areas, CBER staff should be provided with sufficient budget and time (and ability to travel) to support participation in conferences and engage in scientific exchanges. Exchanges/rotation opportunities should include not only other parts of FDA and academia, but other agencies including NIH, Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), CDC, Centers for Medicare & Medicaid Services (CMS), DoD [Defense Advanced Research Projects Agency (DARPA), U.S. Army Medical Research Institute of Infectious Diseases (*USAMRIID*), *Air Force Research Laboratory* (AFRL), etc.], and National Institute of Standards and Technology (NIST). These exchanges should be bi-directional, to also bring in well suited staff from these agencies on details/assignments as well.

Steps should be taken to further expand and diversify training programs to support bringing talented post-baccalaureate and post-doctoral scientists to the agency. In the short-term, it is important to further identify approaches to utilize the ORISE or other existing programs in a more flexible manner. Longer-term solutions have been suggested and new programs are being considered, but addressing the short-term needs is still required. *(see also* Scientific Engagement Report*).*

For more senior scientific staff, consider the following:

1) A sabbatical program for intramural scientists in academic laboratories

2) Assure appropriate travel funding for investigators to stay abreast of emerging technologies.
3) Expand mentorship/professional development program for staff.

IMPACT AND SUSTAINABILITY OF CORE FACILITIES

Key Findings

CBER at the Center level, OBE and other offices each provide critical core facilities to support research initiatives across CBER, and in some cases other parts of FDA. These research resources include the FDA animal facility, "Next Generation Sequencing" (and other biotechnology services), flow cytometry, confocal microscopy, specialized containment labs, and high performance computing infrastructure supporting data visualization, data storage and other capabilities. These facilities and resources (and the experts required to support these capabilities) require continual support, training, maintenance and upgrades.

Recommendations

Sustaining CBER core facilities, including necessary resources and their staff should be a priority. Sustainable funding models for these facilities and outlining their role in supporting broader FDA-wide programs should be carefully developed, including potential support from the Office of the Chief Scientist (OCS) as FDA-wide scientific capabilities.

OFFICE OF BIOSTATISTICS AND EPIDEMIOLOGY

Overview

The Office of Biostatistics and Epidemiology (OBE) provides support to all the offices of CBER and thus its responsibilities are very broad. It provides biostatistical, epidemiological and mathematical expertise to teams of CBER reviewers as they evaluate new products for licensure. In addition, research is conducted to determine the effect of potential new policies and regulations. For example, what would be the effect of replacing the lifetime deferral on blood donation with a deferral of one year for individuals at risk for transmission of HIV?

Many of the responsibilities of OBE go beyond CBER. Therefore, OBE works collaboratively with the other FDA centers when it is appropriate to share expertise and to avoid duplication of efforts. Some of the issues involve broad health issues impacting a large segment of the US population who are receiving vaccines (many are given nearly universally), or blood and blood products. To carry out this mission OBE works with the Department of Health and Human Services (HHS), DoD and CDC. It also collaborates with the World Health Organization (WHO) on global public health problems.

OBE has several exciting research projects. One of OBE's research areas is the use of large patient record databases for epidemiologic studies, such as the safety and efficacy of vaccines and biologic products. Adverse event reports are submitted by the public, medical personnel and manufacturers to Vaccine Adverse Event Reporting System (VAERS) and FDA Adverse Event Reporting System (FAERS). They include both structured fields and free form text that is time consuming to extract manually. There is a very exciting, novel research project on natural language processing (NLP) for to extract information from these text reports. The result will be a quicker, more efficient analysis of potential problems with a licensed product. This NLP system could also be used to search electronic health records, help conduct epidemiological studies and aid in review of new product applications. The NLP system could result in improved surveillance of safety of licensed products post-market when a larger number of people are exposed to the product than during the clinical trials. It may be possible now to identify the responses of specific subgroups and uncover potential risks using large healthcare databases both public and private. Another area is research related to clinical trials including Bayesian methods and adaptive design to enhance the ability to evaluate submissions for licensure. These methods are particularly important in moving beyond rigid requirements for certain designs and approaches which may not be feasible in specific situations.

Findings

Cutting edge research is necessary to advance knowledge as new types of products and new methodologies are developed. It is also essential to anticipate future needs of CBER.

The high-performance computing laboratory enables researchers to use data from next generation sequencing for personalized (or Precision) medicine and to run large scale simulations such as the ones related to the effect of new regulations for blood donation centers.

Recommendations

While it appears that OBE is doing a good job of leveraging its present resources and finding fruitful collaborations with government agencies and academic institutions,

additional resources would allow a greater effort to be applied to artificial intelligence research and the development of the natural language processing system. This project is in the beginning stages and holds great promise for product safety surveillance.

Regulatory demands tend to take time away from research and ways to preserve research time is crucial. In the future, OBE will need to upgrade technology and replace personnel as they leave and add new personnel to fill expertise gaps as they occur. Some of the positions at CBER are postdoctoral fellowships and by their nature temporary. It is necessary to have an appealing workplace with stimulating challenges to attract strong candidates. Potential employees who are considering a job at the FDA are also being pursued by industry where the salaries are much higher and academia where the intellectual challenges are great. To be competitive, the FDA needs to do its best to ensure that there will be time to advance regulatory science and do interesting research and that there will be funding to support this research. Travel to conferences to present research findings and to develop contacts with other researchers is essential and must be supported.

OFFICE OF BLOOD RESEARCH & REVIEW

Overview

OBRR is composed of two main divisions focused on Blood Components and Devices (DBCD) and Emerging and Transfusion Transmitted Diseases (DETTD). This critically important office within the FDA is responsible for review of investigational and commercial use of blood components, related drugs and devices, and devices for the detection of transfusion transmissible pathogens and diagnostic tests for retroviral infections. As such, they regulate the safe production of blood components including the development of procedures and guidance for the blood industry. This office is charged with addressing potential threats to the safety of blood components from emerging infectious agents through preparedness and global public health outreach. Their research program is focused on developing and maintaining a scientific base for establishing methods and standards that ensure continued safety and effectiveness of blood components and devices, development of expertise in all areas of bacteriology, virology, parasitology and prion disease, as well as core knowledge in immunology, biochemistry, cell and molecular biology. The research program has two broad goals to assess and promote the safety and effectiveness of: 1) transfusion products and related devices and technologies and 2) transfusion-transmitted disease agent donor screening, tests and diagnostics.

The research program of OBRR is an excellent example of how regulatory science supports the overall mission of CBER and the FDA. Their research facilitates new product and device development and regulatory evaluation that assures the continued safety of blood components as well as ensuring the highest level of preparedness for emerging pathogenic threats. They have strong global outreach and their work has advanced the field on a global scale. Within CBER, this office demonstrates some of the strongest coordination with manufacturers, public (i.e. blood donors/recipients), and external scientists, and these relationships position them to optimally review and regulate the components and devices within their portfolio. The research program has continued to demonstrate focus and relevance, research quality and breadth and diversity of funding resources.

Findings

The research program office has been highly productive over the past 5 years with 296 peer-reviewed publications and more than $19 million of external funding. One of the most notable accomplishments was their critical role in protecting the safety of the nation's blood supply from the threat of Zika virus by the establishment of an RNA reference standard that facilitated the validation of screening tests for manufacturers, and that has now been implemented nationwide.

Investigators within DBCD have provided new insights on microRNAs as biomarkers of product quality that will enhance strategies to improve the shelf-life of ex vivo stored blood cells. They have also conducted research on oxygen carrying solutions to control or suppress oxidation-related hemoglobin toxicity, enhancements to pathogen reduction systems, and RBC molecular typing to improve transfusion safety. Investigators within DETTD have focused on emerging, re-emerging, terrorism-related and neglected tropical pathogens with the development of novel testing methods and studies of pathogenesis. These efforts have included next generation techniques such as multiplex assays, microarrays and even laser-based detection. Research on improvements of parasite detection have the potential to enhance donor screening

assays for *Trypanosoma cruzi* and *Babesia microti,* and to further development of biomarker assays of parasite vaccine efficacy. All of these research activities relate directly to the stated goals, and support the regulatory functions of the OBRR.

Recommendations

OBRR has an excellent focused research portfolio, but some additional resources could be productively allocated for the focused generation of high throughput sequencing data for generating reference panels for blood group and HLA antigens. In addition, the various NIH-supported large scale human genome sequencing programs should be leveraged for data to inform these efforts.
Collaborations with industry (e.g. SeCore HLA sequence based typing/ Thermofischer) and with academic partners (e.g. Anthony Nolan Trust, UK) could potentially accelerate some of these efforts and limit cost. In order to accomplish this goal, OBRR may need to upgrade technology and hire new Full-time Equivalent (FTE) with the relevant skills. Hiring FTE with expertise and retaining them is important and thus FDA should consider how best to hire and retain promising scientists and other staff, especially those who are otherwise in high demand, such as people with skills in big data informatics and statistics.

Additional FTE could be deployed to expand -omic and bioinformatics expertise for development of disease specific and toxicity biomarkers for different target pathogens, such as Ebola, Zika, Babesia and HIV, in different blood products.

Additional expertise would be valuable for ongoing and completed data modeling of clinical trials for development of new tools for earlier detection of at-risk population characteristics relevant for pathogens such as Zika and Ebola., so they can be identified for triaged drug delivery. These additional FTE may also spur new efforts for vaccine development for some newer pathogens as Zika, for which collaborations with the CDC may be highly effective for this kind of translational work involving OBRR and/or OVRR

OFFICE OF TISSUES AND ADVANCED THERAPIES

Overview

The Office of Tissues and Advanced Therapies was recently reorganized to combine the Office of Cellular, Tissues, and Gene Therapies, the Division of Plasma Protein Therapeutics (Hemostasis Branch and Plasma Derivatives Branch), and part of the hematology review staff in preclinical and clinical review and project management. The Office of Tissues and Advanced Therapies (OTAT) is now under the direction of Dr. Wilson Bryan. OTAT has a diverse mission with the activities in regulation of recombinant coagulation factors, immune globulins, plasma protein therapeutics, chimeric antigen receptor (CAR) T cells and cancer vaccines, gene therapy products, both *in vitro* and *in vivo* genome editing, cell therapies generally, including stem-cell and tissue engineered products. This broad portfolio is in a highly active field with new programs on all fronts of the regulatory spectrum. For example, recent advances in CAR T cell technology have led to marketing approval of the first CAR T cell product for cancer immunotherapy. It is anticipated that the public demand to leverage advances in human genetics and rapid biotechnology developments will put a higher burden on OTAT to keep abreast of the science as these therapies emerge and come to the FDA for approval.

Key Findings

The research mission is very complementary to the regulatory mission through the programs that were reviewed in teleconferences and in the site visit. Areas of focus include microbiology, immunology, cell / developmental and tissue biology, cancer biology, molecular biology and biochemistry as well as adverse event investigations and biotechnology advances. The programs are well-positioned to investigate the rapidly evolving areas under the mission of OTAT, as OTAT scientists are recognized experts in the fields of gene and cell therapy. Additionally, the Office has a goal of advancing the scientific areas related to individual product classes and there is specific expertise related to these product classes, although some opportunities exist to increase depth in emerging product areas.

Strengths:

- Strong programs in several areas of relevant virology research
- Outstanding efforts in stem cell biology
- Emerging programs in informatics and adverse event (AE) reporting
- Significant depth in immunology

Recommendations

Given the current resources, the scientific diversity is outstanding. However, the scientific and regulatory activity for OTAT is evolving rapidly, so added depth in areas covered within the Office would be highly desirable to anticipate future needs.

Assure in strategic and budget planning, appropriate distribution of resources weighted toward emerging and rapidly evolving areas. Consider that the needs may be very different for the Division of Plasma Proteins and Therapeutics versus the Division of Cellular and Gene Therapies. Plans should enable flexing between two different arenas of focus.

Extend collaboration to other divisions in CBER, i.e., common programs with OVRR.

Assure OTAT is a pivotal component of FDA/CBER strategic plan, contributing to broader horizon scanning and having clear alignment with the overall CBER plan.

Improve the portfolio in the rapidly emerging area of Adeno-associated virus (AAV) gene therapy.

Further development of platform technology for enumeration of vector preparations through advancing development of standards or centralized laboratories.

Contribute to understanding the potential impact of and improve assays for possible genotoxicity related to Crispr/Cas9 gene therapy.

Prepare for rapid evolution of stem cell and tissue engineered products with anticipated submission of these types of products for approval to clinical trials and registration in the near-term. Included in this will be expanding leadership and expertise in manufacturing controls, accompanying devices (e.g., product administration/surgical/imaging).

OFFICE OF VACCINES RESEARCH & REVIEW

Overview

The Office of Vaccine Research and Review (OVRR) has extremely broad responsibility not only for vaccines but also for other products, including allergenic as well as phage and live biotherapeutics. This breadth requires attention not only to modifications in older vaccine products but also novel therapeutics which are at the cusp of development. In addition, given the role of vaccines in controlling emerging infections, there is need for rapid, flexible redirection of expertise to assist in development and regulation of such products.

What is now OVRR has a long history of working on development, regulation and standardization of vaccines. Important examples are the *Haemophilus influenzae* type B vaccine and, more recently type A meningococcal vaccine. To be able to fulfill their functions, the researcher-reviewers have available Biosafety Level 2 and 3 laboratories for their use and can indirectly access Biosafety Level 4 laboratories through collaborations. This is particularly necessary in responding to public health threats such as Ebola and Zika. Examples of themes useful both for research and regulatory activities are improvement of potency assays, study of correlates of immunity, and development of animal models. Investigator initiated research is the usual mechanism for implementation of this work. Support generally comes from agency funds, often leveraged with support from collaborating institutions, including other federal agencies such as the Department of Defense and NIH as well as nonprofits such as the Bill and Melinda Gates Foundation.

Key Findings

The reviewers examined several specific research projects including evaluation of cell substrates used in vaccine production, novel methods to detect adventitious agents, rational design of improved mumps vaccines, fecal microbiota transplantation and norovirus growth and detection. These emerging therapies and tools to support vaccine development for pathogens important to the health of the public show recognition of the need to be at the forefront of new challenges to regulation and standardization.

The reviewers were impressed at the ability of OVRR to handle such a broad and evolving range of subjects. The ability of the researcher-reviewer to obtain outside funding and to publish in major journals is evidence of past success. The challenge is to prepare for new technologies which will inevitably be submitted for approval.
Overall, the reviewers strongly support the work of OVRR and encourage its efforts to be ready to respond in an often-challenging environment.

Recommendations

Ability to attract fellows needs to be strengthened given competing opportunities. There needs to be continuing recognition that the requirement that investigators can carry out an assay themselves should not limit consideration of novel techniques being proposed from outside. These techniques could be adopted by FDA investigators if it seems to be useful for their work but there should not be a requirement for them to do so.

Conclusions

The Subcommittee of the CBER Science Board conducted a comprehensive review of the research programs at the Center for Biologics Evaluation and Research (CBER). Following a series of highly informative teleconferences, the committee became familiar with sufficient background information to conduct an in-depth site visit, which included research presentations and interviews with key staff in the research programs as well as FDA leadership. In a closed session and on subsequent teleconferences, groups of reviewers with specific expertise in each CBER office, prepared a written report which was subsequently reviewed by the entire committee. The conclusion of the review committee is that CBER has developed robust research programs which are central to the researcher-reviewer model. The research conducted in each CBER Office, is both highly relevant to the overall CBER mission as well as advancing scientific understanding of important questions on the national and international level. The review committee made detailed recommendations on strategies for cross-FDA and external collaborations as well as emphasizing the need for horizon scanning to anticipate future scientific and public health areas for investigation. The necessary resource management is in place to maximize productivity and the committee recognized several areas for future investment and planned growth. The committee appreciates the challenges faced by all public institutions to properly manage resources and the leadership should be congratulated on the outstanding programs that have been cultivated at CBER and the continued growth of these programs will ensure the success of FDA and CBER into the future.

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Appendix 1. CBER Research Review Subcommittee Roster

Barry J. Byrne, MD, PhD, Subcommittee Chair
Cellular, Tissue and Gene Therapies Advisory Committee
Director, University of Florida Powell Gene Therapy Center
Professor, Pediatrics and Molecular Genetics & Microbiology
Associate Chair, Pediatrics University of Florida College of Medicine

Arnold S. Monto, MD, Subcommittee Co-chair
Vaccines & Related Biological Products Advisory Committee
Thomas Francis Jr. Collegiate Professor of Public Health
Professor of Epidemiology
University of Michigan School of Public Health

Cynthia A. Afshari, PhD, DABT
FDA Science Board
Vice President, Comparative Biology and Safety Sciences
Amgen Inc.

Tabassum Ahsan, PhD (served until 7/25/2017)
Cellular, Tissue and Gene Therapies Advisory Committee
Assistant Professor, Tulane University

Anthony Bahinski, PhD, MBA, FAHA
FDA Science Board
Global Head, Safety Pharmacology
GlaxoSmithKline

Col. Michael R. Nelson, MD, PhD
Allergenic Products Advisory Committee Advisory Committee
Deputy Commander for Education Training and Research
Walter Reed Army Institute of Research

Steven W. Pipe, MD
Blood Products Advisory Committee
Professor, C.S. Mott Children's Hospital
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Bruce M. Psaty, MD, PhD, MPH
FDA Science Board
Professor, Medicine & Epidemiology
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Theodore F. Reiss, MD, MBE
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Sonja S.B. Sandberg, SB, PhD
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Scott J.S. Steele, PhD
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Director, Regulatory Science Programs
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Blood Products Advisory Committee
Associate Pathologist and Director of Blood Transfusion Services
Massachusetts General Hospital

Appendix 2. Charge to the CBER Research Review Subcommittee

Charge to the CBER Research Review Subcommittee

The Center for Biologics Evaluation and Research regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products. CBER regulates a wide range of products from vaccines to cell and gene therapy, blood and blood products and related devices.

CBER Vision for Regulatory Science: To conduct scientific research of the highest quality and relevance, that is integral to the Center's regulatory mission and public health portfolio, proactive and anticipates regulatory and public health needs, and in direct support of CBER's regulatory decision-making and policy development responsibilities.

In 2015, CBER hired McKinsey Consulting Company to review how CBER manages and supports regulatory science. The outcome of that engagement has been to augment management processes with new governance, new tools for communication, and some changes to the way funding is provided to support research programs. CBER performs external peer review of all laboratory programs every four years, and periodically has done broader Center or Office-wide reviews of the scientific program. As we move into our second full year of using the new approaches to manage and govern research at CBER, we now want to evaluate the ongoing overall research portfolio and look strategically to the future research agenda.

Charge to the FDA Science Board: The FDA Science Board is charged with conducting a review to assess how CBER's regulatory science portfolio can best anticipate and address biological products that are emerging or on the horizon, as reflected in ongoing scientific research, as well as new public health concerns from currently marketed biologic products. The subcommittee should consider the broad scientific disciplines and technologies that CBER needs to support its regulatory functions and decision making.

Specifically, the Board is asked to address the following question:

- Comment on how CBER's scientific endeavors support the Center's regulatory mission.

- Given the existing breadth of CBER's current and anticipated future regulatory portfolio and responsibilities, are there changes CBER should make to its regulatory science research portfolio to best accomplish our regulatory and public health mission?

- Assess any gaps in regulatory science capabilities or expertise.
- Identify opportunities for collaboration to better leverage CBER's regulatory science programs.

Appendix 3. Thank you letter to the CBER Research Review Subcommittee

March 17, 2017

Dear Dr. ,

Thank you very much for your willingness to serve on a subcommittee of the FDA Science Board. The subcommittee is essentially charged with performing a broad, high level review of the research program at the Center for Biologics Evaluation and Research (CBER). A detailed charge is included in this package.

We intend to structure this review with a series of teleconferences between the subcommittee and key CBER staff. These teleconferences will provide background information about the research program, including our regulatory mission, the research portfolio, and the benefits and challenges of performing research at CBER. We hope that this series of teleconferences will support the most interactive and productive one-day site visit on June 6, 2017. The one-day site visit will include presentations of specific examples of impactful research and interviews with key staff in the research program as well as leadership. In addition, we will provide time to tour the laboratory facility and for closed sessions to allow the subcommittee to start formalizing key aspects of the report.

Thank you again for your willingness to share your time and expertise in order to help ensure that our research program is optimally configured to support our regulatory and public health mission.

Sincerely,

Peter Marks, MD, PhD
Director, Center for Biologics Evaluation and Research, FDA

Appendix 4. List of all supplemental material provided to the subcommittee

Charge to the CBER Research Review Subcommittee
CBER Research Review Subcommittee Expertise
Thank you letter to the CBER Research Review Subcommittee
FDA Organizational Chart
CBER Organizational Chart
CBER Strategic Plan for Regulatory Science & Research 2012-2016
CBER Interim Strategic Plan FY2017-2019
FDA Strategic Priorities 2014-2018
Advanced Regulatory Science at FDA 2011
Review of Research Program CBER Final Report 1998
CBER Overview Teleconference 1 –Agenda
CBER Overview Teleconference 2 –Agenda
CBER Regulatory Science Council Charter
CBER Resource Committee Charter
Recent Recruitment Efforts for Current and Anticipated Regulatory Portfolio
2016 CBER Training Seminars & Symposia
Cross Office Research Working Groups
Cross Center Research Working Groups
Activities to support development of physical standards and product evaluation tools & methods
Regulatory Guidance Documents (2014-2016)
Public Workshops (2014-2016)
Advancing public health using regulatory science to enhance the development and regulation of medical products: Review article
Office of Vaccines Evaluation & Research Summary
OVRR Principal Investigator Overviews
OVRR Overview Teleconference 3 –Agenda
Office of Tissues and Advanced Therapies Summary
OTAT Principal Investigator Overviews
OTAT Overview Teleconference 4 –Agenda
Office of Blood Research & Review Summary
OBRR Principal Investigator Overviews
OBRR Overview Teleconference 5 –Agenda
Office of Biostatistics & Epidemiology Summary
OBE Principal Investigator Overviews
CBER Overview Teleconference 6 –Agenda
2006 Office of Vaccines Research and Review Site Visit Report
2006 Office of Blood Research and Review Site Visit Report
2006 Office of Cellular Tissues and Gene Therapy Site Visit Report

Appendix 5. CBER Overview Material

CBER Regulatory Science Council Charter (March 7, 2016)

MISSION

The mission of the CBER Regulatory Science Council (RSC) is to serve and advise the Center Director and Deputy Center Director through developing broad, Center-level goals and providing oversight across all of CBER's research activities.

OBJECTIVES

The RSC will:

- Review and recommend strategic decisions impacting Center-wide research goals to the Center Director for approval
- Provide oversight of the Center's research activities to ensure organizational alignment with Center-wide research goals
- Increase cross-Office awareness and coordination of the research portfolio
- Identify ways to continuously improve the state of CBER's scientific research

SCOPE

The RSC will be tasked with the following activities:

- Provide input on Center's research goals
- Work with Office Directors to shape Office goals and objectives and ensure continued alignment with Center's research goals
- Provide input on major policy changes that affect research program (i.e., how budget is allocated)
- Use research dashboard as a tool to oversee and monitor the portfolio down to the project level
- Identify emerging research priorities
- Sponsor and attend Center-wide initiatives to strengthen culture of research (e.g., CBER Science Impact Series, Science Days)
- Liaise with external and internal stakeholders to consistently integrate best practices

MEMBERSHIP ROLES AND RESPONSIBILITIES

Members

The RSC is composed of the following representatives:

- Center Director
- Deputy Center Director
- Center ADR (Chair)
- OVRR, OBRR, OCTGT, and OBE Office Directors or Deputy*
- OVRR, OBRR, OCTGT, and OBE ADRs* (Rotating Vice-Chair: Annual Term)
- OM Director or Deputy Director
- Executive secretary

**NOTE: While an Office Director and Deputy may substitute for one another, one of them must be present; the Office ADR cannot represent an Office alone*

Chair

The Chair has primary responsibility to:

- Confirm meeting agendas in coordination with input from members
- Conduct RSC meetings and direct communication of group information
- Guide the group to accomplish its mission and objectives
- Establish RSC subcommittees and *ad hoc* working groups as necessary
- Track progress of action items

Vice-Chair

The Vice-Chair has primary responsibility to:

- Perform all Chair responsibilities in the absence of the Chair
- Promote involvement and balanced participation of all RSC members
- Assist the Chair in promoting regular RSC member attendance, as necessary
- Provide leadership and direction to RSC, subcommittees and *ad hoc* working groups

Executive Secretary

The RSC Executive Secretary will work closely with the Chair and Vice-Chair to organize the RSC meetings and ensure the effectiveness of RSC governance processes.

The RSC Executive Secretary has primary responsibility to:

- Promote relevant topics and content for agenda topics
- Schedule meetings and communicate agenda prior to each meeting
- Lead the development and prioritization of RSC agendas and preparations
- Follow-up on RSC assignments and action items assigned to RSC members
- Maintain the roster of the RSC its subcommittees, and *ad hoc* working groups

Member

RSC members or designated alternates will:

- Attend RSC meetings
- Prepare for and proactively participate in RSC meetings and activities
- Serve as a catalyst for change and support within the member's area of responsibility
- Actively offer insight and perspective to support and improve the implementation of new initiatives promoted by the RSC
- When called, participate in RSC subcommittees and ad hoc working groups
- When called, lead RSC subcommittees and ad hoc working groups, holding them accountable for developing and executing plans
- Bring non-progressing assignments to the RSC for attention

MEETINGS

- Meets 4 times per year (quarterly)
- One full day planning session and 3 other 2 hours sessions
- Virtual or *ad hoc* forums as needed, with in-person attendance encouraged

DECISION MAKING PROCEDURES

In general, decisions will be determined by consensus. For items that are determined to require formal voting, majority rule will define the outcome.

- Voting members: OBE, OBRR, OCTGT, OVRR
- One vote per office
- Formal votes may be used for the following items:
    - Approval of the initial charter and subsequent amendments to the charter
    - Other items deemed to need voting
- Decisions on budget items will be voted on by the Resource Committee
- The RSC Chair does not vote and cannot overrule votes, but can break ties if necessary.
- The RSC Chair must be present for formal voting. If the RSC Chair is not in attendance, voting will be deferred.
- Decisions endorsed by the RSC will be recommended to the Center Director and Deputy for final approval.

CBER Resource Committee Charter – 4/29/16

Purpose

This charter describes the duties and responsibilities of the Center for Biologics Evaluation and Research (CBER) Resource Committee (RC). This charter also explains the composition of the RC membership and its operating procedures.

The committee ensures that financial planning for CBER is supportive of and fully integrated with the priorities and mission of CBER. The committee provides oversight of fiscal management and guidance to those responsible for CBER's day-to-day operations.

In order to make informed decisions and support effective administration of other financial business, the RC must stay in contact with various groups, including but not limited to the FDA User Fee Council, CBER Information Management Coordinating Committee (IMCC), and CBER Regulatory Science Council (RSC).

Background

The RC was created to improve the transparency and accountability of CBER's budgeting processes. The RC serves as a resource for the Center Director in assessing funding requests, recommending Center-wide policy on resource expenditures and allocations of full-time equivalent (FTE) positions, and informing Center leadership on significant budget issues and key budget metrics.

The establishment of the RC is to provide a structured process for CBER Offices to formulate and justify their annual budget requests to Center leadership and to make funding recommendations to the Center Director based on agreed upon resource policies developed by the RC with the concurrence of the Center Director. The RC is a recommending body for facilitating the Center Director's decision-making responsibilities over resource issues.

Authority and Responsibility

The RC is intended to be a Center-wide forum for discussing and recommending resource management strategies in a manner which aligns with Center and Agency objectives and ensures participation of all CBER Offices. The RC will provide recommendation documents, priority setting, and other work products to the Center Director for decision-making.

The responsibilities of the RC include the following:

- Communicate and educate RC on CBER's financial condition.
- Provide updates on significant budget changes issues or new initiatives.
- Monitor on a regular basis CBER's overall financial operations and conduct annual and periodic reviews addressing topics such as but not limited to:
    - Off-the-top/center-wide expenses
    - Data on Office spending to inform projected budgets
    - FTE allocations
    - PDUFA and PDUFA research-related submissions
- Oversee that timely and accurate financial information is presented to the RC.
- Review of all budget proposals and make recommendations to the Center Director.
- Determine and analyze issues identified by reviews that need to be resolved.
- Establish justification criteria for all funding sources and thresholds for increases. This should include operating and FTE requests and advises Office of Management's Division of Budget and Resource Management on annual budget templates. Work with staff designee to oversee the internal reporting practices meets the RC's need and expectations.
- Review and analyze Offices' proposed annual budget justifications and make recommendations for prioritization of funding requests among Offices (FTEs and Operating Funds) to the Center Director.
- Conduct meeting with Office Directors and Center Director on proposed budget requests.
- Communicate budget decision making to CBER Offices.
- Monitor and review progress and status of CBER's financial operating plan and budget allocations.
- Develop, track, and present key budget metrics for review on a quarterly basis.
- Conduct annual review of financial performance against plan.
- Give updates on other significant budget changes or issues.
- Conduct periodic assessments of contract funding and the value achieved via the contract spending.

- Conduct an annual self-evaluation of the performance of the RC and the effectiveness and compliance with this charter.

Organization
The RC will consist of the following officers: a Chair, Vice-Chair, and Executive Secretary from OM as specified below; and the following additional members: Deputy Center Director, Center Associate Director for Review Management, Center Associate Director for Research, and the Office Director from all Offices.

The Director, Office of Management will serve as Chair; the Deputy Director, Office of Management will serve as Vice-Chair; and the Chief, Resource Management Branch, Division of Budget and Resource Management, OM (or designee) will serve as the Executive Secretary. The OM Director as the Committee Chair will serve as a non-voting member. The Deputy OM Office Director or designee will serve as the voting member for the Office of Management.

One technical expert from each office may attend the committee meeting when the Chair authorizes their attendance.
Deputy Office Directors may attend meetings of the RC either as non-voting participants (in the presence of the Office Director) or as alternate voting members (in the absence of the Office Director.)

Chair
The Chair has primary responsibility to:
- Confirm meeting agendas in coordination with input from members
- Conduct RC meetings and direct communication of group information
- Guide the group to accomplish its mission and objectives
- Establish RC subcommittees and *ad hoc* working groups as necessary
- Track progress of action items

Vice-Chair
The Vice-Chair has primary responsibility to:
- Perform all Chair responsibilities in the absence of the Chair
- Promote involvement and balanced participation of all RC members
- Assist the Chair in promoting regular RC member attendance, as necessary
- Provide leadership and direction to RC subcommittees and *ad hoc* working groups

Executive Secretary
The RC Executive Secretary will work closely with the Chair and Vice-Chair to organize the RC meetings and ensure the effectiveness of RC governance processes.

The RC Executive Secretary has primary responsibility to:
- Promote relevant topics and content for agenda topics
- Schedule meetings and communicate agenda prior to each meeting
- Lead the development and prioritization of RC agendas and preparations

- Prepare RC meeting minutes and document decisions made about each agenda item (actions taken or agreed to be taken, voting outcomes, motions taken or rejected, new business, items to be held over, next steps)
- Follow-up on RC assignments and action items assigned to RC members
- Maintain the roster of the RC, RC's subcommittees, and ad hoc working groups
- Maintain RC SharePoint site

Member
RC members or designated alternates (such as Deputy Office Directors) will:

- Attend RC meetings
- Serve as the voting member for their respective office (except for the Office of Center Director, where the Deputy Center Director will serve as the voting member)
- Prepare for and proactively participate in RC meetings and activities
- Serve as a catalyst for change and support within the member's area of responsibility
- Actively offer insight and perspective to support and improve the implementation of new initiatives promoted by the RC
- Participate in RC subcommittees and ad hoc working groups (as needed)
- Lead RC subcommittees and ad hoc working groups, holding them accountable for developing and executing plans (as needed)
- Communicate non-progressing assignments to the RC for attention

Operating Procedures
The RC will meet quarterly with one of the meetings being a half day annual budget meeting with the Center Director prior to the fiscal year. Ad hoc or virtual forums may be scheduled as necessary. Notice of meetings will be made in a timely manner to RC members.

Any member or their alternate of the RC may propose meeting agenda items. Members are encouraged to solicit suggested agenda items from their staffs. Proposed agenda items should be submitted by RC members to the Executive Secretary at least 10 business days prior to a committee meeting.

The Chair will determine the applicability of a proposed agenda item and decide if it will be submitted to the committee members and included on the agenda. The decision will be communicated to the individual who submitted the proposal.

Meeting agenda and materials will be provided to the RC members in advanced of the committee meeting.

Meetings will be summarized in writing promptly after they are held. At a minimum, summaries should record issues presented, decisions made, the rationale for those decisions, and any outstanding actions items. Committee members will review meeting summaries and provide comments within the requested timeframe. Absence of a reply within the requested timeline will be considered as concurrence. The summaries will be posted held in a file maintained by the Executive Secretary as well as posted in a location accessible by RC members.

The Chair or Vice-Chair will assure that decisions, issues, action items, etc. attributable to the committee are documented and communicated to management and staff, as appropriate, in a timely manner. These items will be sent to committee members before being posted.

Voting Procedures for Making Recommendations
Although consensus will be the goal, in cases where a vote is necessary, only members or their alternate will be permitted to vote (one vote per Office including the Office of the Center Director). The Deputy Center Director or designee will be responsible for voting.

When votes are taken, a simple majority is needed. Offices may abstain from a specific vote. The votes will be noted in the summaries. The Chair or Vice-Chair will escalate issues to the Center Director, if needed.

Working Groups
Working groups may be established by the RC for the following purposes:

- The committee identifies a need based on factors such as its knowledge of CBER operations and policies or new procedures and innovation.
- The Center Director, or designee, directs the committee to establish a new working group to achieve specific objectives (e.g. developing a recommendation on CBER-wide resource expenditures (such as scientific maintenance agreements).

Working groups will have a limited lifetime. The working group will adjourn when:

- It has successfully completed its goal or,
- Additional work is not required from the Working Group as determined by the RC. Each group will be responsible for:
- Confirming its objectives with the RC.
- Defining member responsibilities.
- Providing work products to the RC in a timely manner.

Working Group Organization

Each working group will have a Chairperson selected from within the RC who will direct the group's activities. The Chairperson should have a working knowledge in the area of responsibility of the working group. It is desirable to have at least one member of the RC on the working group where possible.
The working group chairperson will be appointed / approved by the RC. The RC members will ensure their office identifies appropriate working group members in a timely manner, whenever needed. Member selection will be based on office affiliation, qualifications, expertise, ability to contribute to the expert working group and current workload as identified by each individual's supervisor. Each office will have the option of deciding their office's representative. Some working groups may contain representatives from other groups within the Agency or Center to provide needed expertise. Working group membership will generally be kept small (e.g. six to eight members).

Working group members are responsible for:

- Attending the working group meetings;
- Representing their view to the working group;
- Communicating the discussions of the working group to their Office management and obtaining input from their Offices for communication to the working group.

Subcommittee Organization
RC subcommittees may be established to perform ongoing activities and work products with oversight by RC. Unlike working groups, once a subcommittee is formed it has an indefinite lifespan.
The RC's subcommittees may be formed for any purpose but typically perform ongoing activities that are more detailed or technical than the strategic activities of the RC. The RC ensures subcommittee activities are consistent with strategic objectives and provides an escalation path for issues.
The RC proposes RC's subcommittees to the Center Director. The Center Director, or designee, approves the subcommittee and authorizes the ongoing resources that are needed.

The RC will be responsible for:
- Defining subcommittee responsibilities and authority;
- Defining the path for escalation of decisions and issues;
- Providing the subcommittee with priorities, mandates, resource constraints, and other requirements necessary for the subcommittee to perform its duties.

Each RC's subcommittee will be responsible for:
- Confirming its objectives and scope of activity with the RC.
- Defining membership and member responsibilities.
- Escalating decisions and issues to the RC, as needed.
- Tailoring activities in accordance with the priorities, mandates, resource constraints, and other requirements communicated by RC.
- Responding to RC requests in a timely manner.
- Providing regular progress/status updates to the RC.

Subcommittee Organization

Each subcommittee will have a Chairperson who will direct the group's activities. The Chairperson should have a working knowledge in the area of responsibility of the subcommittee. The subcommittee chairperson will be appointed/approved by the RC. The remaining membership and organization of the subcommittee will be proposed by the subcommittee and approved by the RC and the Center Director, or designee.
This Charter will be continually revised as needed based on experience gained in the use of the RC.

Recent recruitment efforts for current and anticipated regulatory portfolio

Office	Principal Investigator	Year Recruited	Recruited from	Research Area	Program Title
OVRR	Gabriel Parra, PhD	2015	National Institutes of Health	Vaccine development for emerging pathogens (e.g., norovirus)	Understanding Norovirus Diversity and Immune Responses to Inform Vaccine Design
OVRR	Paul Carlson, PhD	2014	University of Michigan	Using the microbiome to treat antibiotic-resistant bacterial pathogens	Identification of targets for development of vaccines and non-antibiotic therapies against gastrointestinal pathogens
OTAT	Kyung Sung, PhD	2015	University of Wisconsin	Using microphysiologic systems to improve safety and effectiveness of tissue-engineered medical products	Investigating the effects of cell-materials interactions on the safety and effectiveness of cell-based products.
OTAT	Zhaohui Ye, PhD	2015	Johns Hopkins University	Mechanistic studies for understanding and controlling directed cellular differentiation of induced pluripotent stem cells (iPSCs) and effects of the gene editing endonuclease Cas9 on genome integrity and differentiation function when used in human iPSCs.	Efficacy and safety of stem cell-based gene and cell therapies
OVRR	Haruhiko Murata, MD, PhD	2015	Food and Drug Administration	Tools to access the quality and effectiveness of high priority vaccine targets	Development of Tools to Assess Human Cytomegalovirus (HCMV)

					Neutralization and Cell Entry
OTAT	Nirjal Bhattarai, PhD	2015	University of Iowa	Factors that influence T cell activation and how that might inform evaluation of CAR-T cell-based therapies (CAR, Chimeric Antigen Receptor)	Development of Gene and T cell Therapy Products Based on RNA Viruses

2016 CBER Training Seminars and Symposia

Event	Description
High-performance Integrated Virtual Environment (HIVE): A Next Generation Sequencing Analytical Solution for Research and Regulatory Use Training	The High-performance Integrated Virtual Environment (HIVE) is a high-throughput cloud-based infrastructure developed for the storage and analysis of nucleotide sequencing data and associated biological meta-data. HIVE consists of a web-accessible interface for authorized users to deposit, retrieve, share, annotate, compute and visualize Next-generation Sequencing (NGS) data in a scalable, secure and highly efficient fashion. Resources available through the interface include algorithms, tools and applications developed exclusively for the HIVE platform, as well as commonly used external tools adapted to operate within the parallel architecture of the system.
Introduction to Risk Assessment for Biologics	This course provides the four-part risk assessment framework developed by the National Academy of Sciences that includes: hazard identification, hazard characterization, exposure assessment and risk characterization, and its application to critical biologics regulatory questions.
CBER Science Impact Series	The objective of the CBER Science Impact Series is to engage Center/Office leadership and research as well as non-research staff to improve understanding of CBER's regulatory science program, why CBER engages in mission-relevant research, and how CBER's regulatory science program impacts the Center's regulatory mission and public health. Two principle investigators present monthly at this series.
CBER Science Symposium	The objective of the CBER Science Symposium is to highlight the research CBER does and provides an opportunity for scientific exchange across the spectrum of the products regulated by our center.
Division of Viral Products Seminar Series	This seminar series is designed to update attendees on recent advances in the general areas of virology, microbiology, toxicology, biomedical engineering, nanotechnology, and infectious diseases**.**
Office of Blood Research & Review Hematology Science Lecture Series	OBRR Seminars focus on ongoing and published research, physiology, pathogenesis, and clinical practice related to the safety and efficacy of the blood products regulated by the FDA. Presentations cover mechanisms of action and adverse events related to administration of our products, regulatory issues as they pertain to clinical practice, trial design, biostatistics, and pharmacokinetics.

OTAT Seminar Series	The objective of the OCTGT Seminar Series is to present current research on issues related to the development of cell and gene therapies.
OBE Seminar Series	The OBE Seminar Series provides staff with in-depth training in areas of clinical trial methodologies, design and analyses of post-marketing studies, safety evaluations, and benefit-risk assessment. Prominent academic experts are invited to speak on recent developments, current controversies, and emerging trends in specific fields.
DBPAP Seminar Series	This seminar series is designed to update attendees on recent advances in the general areas of bacteria, parasitic, and allergenic products.

Cross Office Research Working Groups

Ebola Working Group	The Ebola Working Group is a forum for discussion on scientific ideas regarding Ebola research projects within CBER and allows for possible collaborations/reagent sharing.
Zika Working Group	The Zika Working Group is a forum for discussion on scientific ideas regarding Zika research projects within CBER and allows for possible collaborations/reagent sharing.
CBER Genomic Working Group	The CBER Genomics Working Group is a forum to discuss issues regarding genomics and NGS data used in regulatory submissions. Updates from this working group inform the FDA Genomics Working Group and vice versa.
Emerging Regulatory Science Biologics Committee (ERSC)	The EBSC provides a forum for Offices and Centers to communicate current and emerging regulatory and scientific issues that arise with regard to regulated biological products including, but not limited to, cell substrate safety, adventitious agent detection methods, and pathogenesis of various emerging and re-emerging pathogens and technologies used to evaluate or manufacture regulated products. The EBSC facilitates collaboration, scientific information exchange, methods and reagent sharing in order to avoid redundancy in research efforts and when possible, fosters the development and implementation of relevant regulatory policy, by promoting communication and coordination of scientists across administrative boundaries.
Biologics Research Coordinating Committee (BRCC)	The BRCC will provide a recognizable structure where research issues can be discussed, coordinated and solutions proposed using standard procedures designed to assure consistency and cross-office involvement. The BRCC is not intended to replace the decision-making responsibilities of CBER management, which will have the final authority on policy issues.

Cross Center Research Working Groups

Working Group	Description
Social and Behavioral Sciences Subcommittee	Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products.
Genomic Working Group	The scope of the GWG is to prepare FDA to address IT and scientific challenges to facilitate FDA readiness for Next Generation Sequencing data.
Modeling and Simulation Working Group	The main objectives are to raise awareness regarding the types and uses of M&S in regulatory science research and applications; to support the implementation of M&S in the regulatory process; develop mechanism (e.g., roadmap) for establishing credibility of M&S used for regulatory decision making; and create a community to foster and support collaborations, share expertise, and collate resources, where appropriate.
The Toxicology Working Group	The main responsibility of the Toxicology Working Group is to create an environment for enhanced communication and coordination on cross-cutting toxicology activities at FDA or on interagency toxicology-relevant activities.
The Biomarkers Working Group	The mission of the FDA Biomarker Working Group (BWG) is to promote communication across FDA on scientific issues related to biomarker development and regulatory acceptance; to identify process and policy enhancements that may help address challenges; and to coordinate activities and leverage resources impacting multiple Centers.
The Microbiome Working Group	The MWG will identify process and policy areas that may be affected by human microbiome issues, and coordinate microbiome-related activities that impact multiple Centers. In line with these goals, the MWG is also committed to educating the agency on the emerging role of the microbiome in human development and health, as well as how changes to the microbiota that comprise the microbiome through disease or toxic insult can have an impact on the homeostatic mechanisms that maintain its viability.
The FDA Statistics Association	The FDASA will serve as a collective voice in promoting the advancement of statistical sciences within the regulatory environment of the FDA. It will also provide a forum for members to address issues specific to the concerns of all FDA statisticians and foster FDA-wide consistency and harmonization on crucial regulatory statistical issues**.**
The Genetic and Genomic Team	The FDA GGT is a collaborative scientific and policy interest group, focused on professional development, communication improvement, and discussions of scientific and regulatory challenges related to Genomics, Genetics, Proteomics, cutting edge technologies in regulatory submissions and research projects being conducted in various FDA Centers.
The Nanotechnology Task Force	The mission of the NTF is to leverage FDA scientific expertise and resources to advise agency and center leadership on critical and cross-cutting nanotechnology related issues in order to support the development of safe and effective FDA-regulated products.
Additive Manufacturing Working Group	Additive Manufacturing (AM), commonly referred to as 3D printing, is a manufacturing technology that is increasingly being used to produce medical devices and drugs and shows significant promise for biological products. The FDA AM Working Group provides a forum for members (CDRH, CBER, CDER, ORA, and NCTR) to discuss diverse issues related to AM: including medical device printing, pharmaco-printing and

	bio-printing, share ideas and information, collaborate on related initiatives, and enhance communications across Centers and Offices.
The Emerging Technologies Working Group	The mission of the Emerging Sciences Council (ESC) is to leverage scientific expertise and resources to conduct long range horizon scanning to advise agency and Center leadership on how emerging issues and cross-cutting scientific advances may impact FDA preparedness and trans-agency activities. The key responsibility of the WG is to Identify emerging issues and cross-cutting scientific advances that may impact FDA preparedness and trans-agency activities by consulting with others inside and outside government.
The Senior Science Council	The Senior Science Council (SSC) is an Agency forum comprising FDA scientific leadership from the centers and Office of the Commissioner component offices. SSC provides advice and guidance to Agency and center leadership on cross-cutting regulatory science issues, including planning, reporting, programs, policies, and communication. The SSC is not intended to replace the decision-making responsibilities of Agency Office and Center Directors, who have the final authority on science and policy issues relating to science and research.
Committee For The Advancement of FDA Science	Committee For The Advancement of FDA Science (CAFDAS) is an internal advisory committee to the Commissioner, the Associate Commissioner for Science, and the Senior Science Council, addressing FDA-wide science issues from a scientist's perspective, functioning independently of center or discipline.
FDA Fellows Association	The FDA Fellows Association (FFA) serves as a community to represent the interests of all FDA fellows. The FFA works to foster cooperation and collaboration among FDA fellows and assists in promoting scientific communication between fellows and with the FDA scientific community at large

Physical Standards Activities to Support New Tools & Methods (2016)

Activity area	Physical Standards Activity Summary
OBRR	
Adventitious agent test methods for evaluating blood safety	CBER scientists are investigating the appropriateness of sample selection to perform blood screening assays. CBER scientists have performed studies in partition of virus (WNV, HCV, DENV and ZIKV) in blood components.
Adventitious agent test methods for evaluating vaccine safety	CBER staff are completing a study previously funded by NIAID, NIH, to investigate the susceptibility of cell lines (manufacturing "substrates") to infection with the agent of bovine spongiform encephalopathy (BSE) agent and human-derived variant Creutzfeldt-Jakob disease (vCJD) and sporadic CJD (sCJD) agents.
Assays for analysis of cell membrane and protein microparticles and nanoparticles	CBER scientists are developing analytical methods for characterization of protein particles in blood and plasma products, as well as in other protein and peptide products where product particles are investigated for involvement in the product adverse effects.
BSL2 test to assess potency of Filovirus vaccines and convalescent plasma for treatment of filovirus disease and evaluation of potency of hepatitis A virus immunoglobulin preparations.	CBER scientists are developing BSL-2 test to assess the potency of candidate Filovirus vaccines. To do so, researchers are comparing total antibodies, neutralizing antibodies, and cellular immunity induced by vectored and subunit Filovirus vaccines. These assays will also be used to evaluate total and neutralizing anti-GP antibodies in plasma of ebolavirus convalescent patients to assess immune responses and efficacy of treatment of acute ebolavirus patients transfused with convalescent blood, plasma, or immunoglobulin preparations. CBER scientists are also performing a field test evaluation of the Ebola virus antibody assays in Sierra Leone in collaboration with the Italian National Institute of Infectious Diseases "Lazzaro Spallanzani." CBER scientists have used their hepatitis A virus (HAV) neutralization assay based on a recombinant virus containing an antibiotic selectable marker to evaluate the potency of anti-HAV immunoglobulin preparations (IG), and have implemented pharmacokinetic models to estimate the efficacy period of currently used preparations worldwide. CBER scientists determined that currently used IG have low potencies including the GamaSTAN, which is the only licensed IG in the US indicated for HAV infection.
Identification of microbial contaminants	CBER scientists have developed cell lines expressing human TLRs which has been used for the identification of microbial contaminants in a product developed for human use. The contaminant identified was E. coli derived flagellin, which was the likely cause of fatality and serious adverse events in an IND study. The sponsor was notified and able to modify the manufacturing process so that the flagellin could be removed.
New assay for detecting viruses	CBER researchers are using pathogen-specific oligonucleotides and oligofluorophores in a multiplex assay specific to the detection of HIV, HBV, HCV, HEV, DENV, and WNV. The detection assay demonstrated specificity and sensitivity with no cross-reaction observed. The simultaneous detection of multiple pathogens with a single test that demonstrates high sensitivity and

	specificity will immensely aid in addressing the health care burden these pathogens place on the national and global health care systems.
Novel technologies for diagnostics; reference panels for HIV	CBER scientists developed multiple assays for detection of HIV, influenza and biodefense pathogens using microarray and nanotechnology methods. Whole genomic arrays that utilize gold nanoparticles and silver enhancement have been developed for multiplexed detection of different influenza strains, Ebola, Marburg and Lassa viruses and HIV. Next Gen sequencing based diagnostics is being developed for detection of a number of different blood borne pathogens. These assays demonstrate proof-of-concept that these technologies can be used to improve the efficiency of testing through highly multiplexed formats. For protein detection, gold and fluorescent Europium nanoparticles have been used to improve sensitivity of current ELISA methods. The technology is being used to develop HIV incidence assay that have improved accuracy and sensitivity. Co-detection of HIV and TB is also being studied to facilitate disease detection of these two common co-infections in AIDS patients.
Pathogen reduction of platelet and plasma products	Bacterial contamination of platelets remains a threat to transfusion recipients. Commercially developed pathogen reduction systems utilize UV light and chemical photosensitizers to inactivate bacteria, viruses and protozoa. However, these methods can damage the transfusion products and may also have inherent toxicities. CBER scientists are developing pathogen reduction systems that utilize naturally occurring molecules which can be excited by UV light to generate free radicals for efficient pathogen inactivation.
OTAT	
Additional tests for evaluating quality of Factor VIII products	CBER scientists developed a methodology to analyze this impurity in FVIII products. It is expected that in future, a method, based on our assay, will be used in an quality testing of FVIII products, in addition to the methods already used by the manufactures. This will result in improving safety and efficacy of current and emerging FVIII products.
Adventitious agent test methods for evaluating safety of human tissues and biologics	CBER scientists are working to develop: the non-biased high throughput sequencing capability using latent infections of EBV in human peripheral B lymphocytes as a model system for detecting occult viral infection; computational methods for identification of specific DNA signatures suitable for developing into Real-Time PCR assays by whole genome Sequence analysis approaches (the PCR assays targeting high risk of bacteria and Candida pathogens are intended for safety improvement of human tissues); multiplex real-time qPCR array for simultaneous detection of eight human blood-borne viral pathogens that threaten safety of human tissues intended as grafts.

Examining the impact of codon optimization, developing computational gene-specific prediction methods; investigating the effect of large PEG molecules	CBER scientists are working to conduct a comprehensive investigation on the consequences of genetic variation in recombinant biologics by customizing Western blotting techniques and developing partial trypsin digestion assays, LC/MS/MS-based sequencing mass spectrometry, Circular Dichroism Spectroscopy, in vitro translation and ribosome profiling to optimize quantification/evaluation techniques. In addition, the incomplete and out-of-date codon usage tables are employed in academic research and industrial design of codon optimized, recombinant therapeutics. Adopting these inaccurate datasets may very likely alter the safety and efficacy of these biologics. Thus, we have created new codon usage tables for all organisms in GenBank using the expanse of recently generated sequencing data. Additionally, a publicly available web interface is under development. Also, CBER Scientists are generating are generating a comprehensive, user friendly tool to study the consequences of genetic variation in disease manifestation and recombinant therapeutics and a dataset of mutations with known phenotypic outcomes and the framework for a functional prediction tree have been created. Finally, since both immunohistochemistry and serum markers are being explored to understand nephrotoxic and hematopathologic effects of these molecules which are incorporated into an increasing number of therapeutic proteins, CBER scientists are conducting studies to determine the suitability of a guinea pig model to evaluate toxicities of intravenous high molecular weight PEO (polyethylene oxide) and PEG.
Gene marker of product characterization, in vitro assays for product potency and in vivo correlates	CBER scientists have identified 78 gene markers of human MSC aging based on cellular expansion by microarray gene expression profiling,. Additional work is being completed to correlate the gene expression data with two different cell proliferation assays. Likewise, similar work and methods are being applied to evaluated MSC miRNA expression.
Immune globulin thrombogenicity and coagulation factor potency methods	CBER scientists developing new and improved coagulation factor potency and thrombogenicity methods to identify thrombogenic impurities in immune globulin products and Factor IX concentrates, measure potency of coagulation factor concentrates, including novel long-acting factors VIIa, VIII and IX and determine the quality of hemostatic factors in plasma for transfusion, including frozen, lyophilized and spray-dried. These methods of biologics' characterization are based on the global hemostasis assay thrombin generation test (TGT). Although TGT is widely used in preclinical and clinical product development, acceptance and utility of the TGT are limited by the lack of assay harmonization and confirmed predictive value in clinical applications.

Improved characterization of MSCs (multipotent stromal cells)	CBER scientists are working to improved methods of cell therapy product characterization. A major effort is work with the MSC consortium, a group of 7 Principal Investigators in DCGT who are pursuing the goal of improved characterization of MSCs (known as mesenchymal stem cells or multipotent stromal cells). The goal has been to develop relevant, useful in vitro assays to assess the function of candidate human MSC-derived products. Another area of effort is improvement of flow cytometry by development of methods to quantify cell surface antigens.
Potency test for influenza vaccines	CBER researchers are working on the refinement of the label-free mass spectrometry method that enables simultaneous identification and quantification of HAs, neuraminidase, and other viral proteins and protein impurities in influenza vaccine. The method is based on LC/MS(E) analysis of tryptic digests of sample and a known quantity of protein standard from which a universal response factor is generated and applied to calculate the concentration of proteins in the mixture. This method can be used to measure the absolute quantity of HA as well as relative quantities other viral proteins and impurities in preparations of whole virus and monovalent vaccine, providing data to demonstrate strain-dependent differences in the amount of NA.
Prediction immunogenicity to therapeutic proteins	CBER scientists are developing computational and in vitro methods for the prediction of immunogenicity to therapeutic proteins.
Adventitious agent test methods for evaluating vaccine safety	CBER scientists are investigating broad nucleic acid based technologies for detection of known and novel viruses for evaluating cell substrates and product safety. CBER scientists evaluated PCR-Electrospray Ionization Mass Spectrometry (ESI-MS) System and virus microarrays for investigations of vaccine-related cell lines. Efforts are ongoing for evaluating next generation sequencing (NGS) for broad virus detection. As an initiative of the Advanced Virus Detection Technologies Interest Group, CBER scientists along with two others from the vaccine industry, have completed virus spiking studies to determine the sensitivity of NGS detection of different virus types using different background matrices. These results provided the basis for current large scale preparations of virus reference stocks that will be available for evaluating NGS for improving safety of biological products. Furthermore, in-house NGS analysis provides first-hand experience with challenges of bioinformatics analysis of large datasets including data management, transfer, and storage. The recent discovery by CBER scientists of a novel rhabdovirus in Sf9 insect cells helped develop a bioinformatics strategy for novel virus detection and led to the development of a new virus reference database for enhancing NGS big data analysis for novel virus detection. The reference materials will facilitate use of NGS for known and novel virus detection for cell substrate characterization and product safety and aid in decision-making and policy development regarding use of NGS in regulatory applications.
Adventitious agent test methods for evaluating vaccine safety	CBER scientists identified improved parameters for adventitious agent detection using next generation sequencing methods.

OVRR	
Efficacy of novel dengue vaccines	A case of "dengue" in a vaccine or control is defined as fever of two days duration plus dengue virus isolation OR the identification of NS1 in blood. The current ELISA to detect NS1 is non-specific for serotype of the infecting virus. CBER scientists are developing a an serotype-specific ELISA assay.
Evaluation of the safety of cell substrates	One of the concerns with using tumorigenic cells or cells derived from human tumors is the presence of residual DNA from the cell substrate in the vaccine. Such DNA could be infectious or oncogenic. CBER scientists are evaluating methods used in vaccine manufacture that could inactivate DNA.
HCMV-neutralizing activity in therapeutic immunoglobulin products	CBER scientists developed a RT-qPCR-based assay which is being modified to assess HCMV neutralizing activity associated with commercial immunoglobulin preparations. This high-throughput RT-qPCR-based HCMV neutralization assay will be useful for facilitating HCMV vaccine development by providing an improved tool for conducting sero-epidemiology studies and measuring immune responses in vaccine trials. CBER scientists are also working to develop an HCMV entry assay based on recombinant VSV-G pseudotyped viruses; if successful, this approach could also be adapted to high-throughput assays for measuring vaccine immunogenicity and activity associated with biological products.
Improvement of Rabies vaccines and the Rabies vaccine potency assessment	CBER scientists have optimized conditions for preparation of the rabies virus strains CVS11 and CVS24 stocks for the virus challenge studies in animals and participated to the International Collaborative Study for alternative ELISA potency testing of rabies vaccines for humans. The goal of this collaborative study was to perform a multi-laboratory evaluation of different sandwich ELISA assays for the quantification of virus-associated GP in inactivated human rabies vaccine preparations. The study organized by the National Institute for Biological Standards and Control (NIBSC) was carried out in December 2014 - May 2015. CBER scientists are also conducting a research on development of alternative (in vivo) serological potency test(s) for the immunogenicity assessment of rabies vaccine.
manufacturing consistency and safety testing	CBER scientists are working to identify markers of virus neuroattenuation. CBER scientists have found that replacement of the nucleoprotein (N), matrix (M), hemagglutinin-neuraminidase (HN) and large (L) genes on an individual basis lead to a 25-50% reduction in neurovirulence. The specific nucleotide/amino acid differences between the attenuated vs. virulent forms of these genes/proteins are being investigated. CBER scientists are also working to identify host factors targeted by the virus and have found that a single amino acid substitution in the mumps virus V-protein that disrupts the ability of this protein to interact with STAT3 leads to virus attenuation. In addition, CBER scientists are studying the efficacy of mumps vaccine. CBER scientists have determined that recent outbreaks in highly vaccinated populations are not likely due to vaccine escape, but rather waning immunity.

Methods of assessing potency of allergenic extracts	CBER scientists are conducting studies on the mass spectrometry-based proteomic approach towards standardization of allergenic extracts.
Molecular consistency of viral vaccines	CBER scientists are using a deep-sequencing approach to monitoring genetic stability and molecular consistency of live and inactivated viral vaccines is being developed. In the past year the work has focused on Oral Polio Vaccine and both live attenuated and inactivated Influenza virus vaccines.
Neutralizing antibody responses against measles virus	CBER scientists have developed a high throughput neutralization assay to measure neutralizing antibody responses against measles virus using a recombinant measles virus expressing enhanced green fluorescent protein (measles-eGFP). Measles neutralizing antibody is a correlate of protection against infection and disease and this automated assay provides a rapid and high-throughput method for measuring these antibody responses during clinical trials and as part of the surveillance effort to eradicate measles worldwide.
Potency test for influenza vaccines	CBER scientists have been working to evaluate the use of isotope-dilution mass spectrometry (IDMS) for quantification of HA in influenza primary liquid standards (pLS). CBER scientists have completed analysis of several primary liquid standards (pLS) by IDMS. Comparison of the IDMS data and results generated by the traditional SDS-PAGE/densitometry method, suggests IDMS may be used in place of the traditional method. In addition, CBER scientists have developed an antibody-independent mass spectrometry (MS)-based potency method. Size-exclusion chromatography (SEC) is being used to separate trimers and multimers of HA, and then IDMS is used to quantify the oligomeric HA. The ability of this approach to accurately quantify influenza vaccine potency is currently being tested; (iii) CBER scientists continue to explore the use of hydrogen-deuterium exchange (HDX) mass spectrometry to quantify the antigenic form of influenza antigens.
Potency test for influenza vaccines	CBER scientists have developed an antibody independent, simple, high throughput receptor-binding SPR-based potency assay, which does not require any reference antisera and could be used for rapid HA quantitation and vaccine release in pandemic scenarios.
Potency test for influenza vaccines	CBER scientists are developing new potency assays for influenza vaccines using ELISA-based technology. CBER scientists are characterizing the reactivity and neutralizing activity of a large panel of monoclonal antibodies that are being generated for use as reagents for the new potency assay. Monoclonals with broad reactivity may be especially useful reagents for use in assaying HA from emerging strains, before type-specific antibodies are available.
Potency test for influenza vaccines	CBER scientists are working to optimize the conditions purification of bromelain cleaved HA (BHA) from different subtype influenza vaccine candidates. This optimization is critical on the quality of the HA antigens used

	as immunogen for preparation of sheep reference antiserum for influenza vaccine standardization.
Safety test for pertussis vaccines	CBER scientists are developing an in vitro test to detect residual pertussis toxin in acellular pertussis vaccines that contain detoxified pertussis toxin as a major component. CBER scientists are determining the sensitivity of this test compared to the animal test that is currently used to detect active pertussis toxin. Ultimately, the goal is to replace the animal test with this in vitro test, thus reducing the number of animals used in the safety testing of acellular pertussis vaccines.
Serologic assays for meningococcal vaccines	CBER scientists have developed a human complement serum bactericidal assay for serogroup A and developing assays to examine breadth of coverage of subcapsular serogroup B meningococcal vaccines that are currently in human clinical trials.
Standardized and non-standardized allergen extracts	The multiplex allergen extract potency assay (MAEPA) which was developed by CBER scientists has been applied to short ragweed pollen and cat hair allergen extracts and to German cockroach allergen extracts.

Appendix 6. Office Overview Material

Office of Biostatistics and Epidemiology

OBE Mission Statement

To protect and improve public health by improving evaluations of product efficacy and safety in clinical trials through the use of innovative trial designs (including adaptive designs), biomarkers, and safety signal detection. Enhancing the use of healthcare data to improve safety and effectiveness monitoring of licensed biological products. Enhancing statistical data analyses, patient input and mathematical modeling for better benefit-risk assessments of regulated products.

OBE Activities

- Work collaboratively with CBER product offices (OBRR, OTAT, and OVRR) to review and evaluate statistical and epidemiological contents in all INDs, BLAs, and other regulatory submissions
- Communicate frequently and work collaboratively with CBER offices and OBE counterparts in CDER and CDRH on development of guidance, policies and procedures
- Conduct research activities related to clinical trial design and analysis, including adaptive and Bayesian trial designs, innovative designs and simulation
- Conduct postmarket surveillance of licensed biologics including review of adverse event reports, safety summaries, sponsor pharmacovigilance plans, study protocols, presentations at FDA Advisory Committees
- Develop benefit-risk assessments and related modeling and simulations
- Use Sentinel including the Postlicensure Rapid Immunization Safety Monitoring System (PRISM) and BloodSCAN to conduct postmarket surveillance and epidemiological studies to address regulatory needs
- Use Center for Medicare & Medicaid Services data to conduct safety surveillance and research on vaccine effectiveness and biologic product safety
- Use High-performance computing systems and develop methods for next-generation sequencing, support laboratory data analysis, conduct simulations
- Encourage and support professional development for regulatory review, research, and business support staff

OBE Research Goals & Objectives

Goal 1: Improve evaluation of product efficacy and safety in pre- and postmarket settings through research on biomarkers, bioassays, adaptive designs and other innovative statistical approaches.

***Objectives*:**

- Research applications of Adaptive and Bayesian clinical trials designs for biologic products.
- Research applications of meta-analyses for rare outcomes to improve assessments of safety of biologics.
- Provide collaborative statistical support for researchers from other units within CBER.

Goal 2: Improve the use of healthcare data to enhance monitoring of the safety and effectiveness of licensed biological products.

Objectives:

- Advance postmarket safety surveillance through methods development and deployment of data mining, text analytics and other approaches, such as use of high performance computing, using data streams such as adverse event reports, claims databases and electronic health records.
- Develop methods to assess of postmarket effectiveness and adverse events for regulated products.
- Develop and apply quantitative bias analysis methods.

Goal 3: Improve analyses and benefit-risk assessments of regulated products by developing enhanced statistical methods, mathematical modeling and computer simulation, and patient input methods.

***Objectives*:**

- Improve benefit-risk assessment methodology development and application of quantitative approaches for regulatory review.
- Advance application of quantitative pharmacokinetic-pharmacodynamic (PK/PD) and related modeling approaches to evaluate dosing regimens and product effectiveness.
- Develop systems biology models of the immune response, infection or vaccination using high performance computing, as appropriate.
- Improve high performance computing and advanced computational methods to support use of Next Generation Sequencing in CBER and FDA research and regulatory missions.

OBE Regulatory Portfolio

OBE staff collaborate with all CBER offices and is responsible for the review and evaluation of statistical, epidemiological, benefit-risk assessment, modeling and simulation issues in the regulatory submissions of the full spectrum of biologic in the portfolios of OBRR, OTAT and OVRR.

Anticipated Activities (horizon scanning)

In meeting FDA performance goals for the Prescription Drug User Fee Act (PDUFA) for fiscal years 2018-2022, OBE anticipates making regulatory and research contribution in the areas of:

- Evaluation of human data on biomarkers for establishing surrogate endpoints for clinical studies
- Innovative uses of adaptive designs, evaluation of novel endpoints, and application of new approaches to statistical analysis in development of drugs for rare diseases
- Use of real world evidence for use in regulatory decision making
- Incorporation of patient's voice in drug development and decision-making
- Benefit-Risk assessment in regulatory decision-making
- Model-informed drug development
- Complex innovative designs in regulatory submissions
- Analysis of data standards for product development and review
- Postmarketing safety evaluations – including Sentinel

Office of Tissues & Advanced Therapies

OTAT Activities

- Perform regulation of advanced therapies and related outreach
- Conduct research in regulatory science
- Contribute to CBER-wide and FDA-wide activities (research management system, FDA Fellows Association, other campus-wide committees
- Participate in the wider scientific community by reviewing manuscripts and grant proposals, editing, participating in and organizing scientific conferences
- Engage in mentoring of staff and trainees and support of their professional development
- Conduct regulatory review of applications for investigational use and product approval for marketing, within PDUFA and MDUFA timeframes
- Develop regulatory policy and issue guidance
- Perform inspections and assist in compliance actions including court cases
- Engage in extensive pre-submission communication with sponsors/applicants (pre-IND and pre-pre-IND advice)
- Engage in stakeholder outreach through workshops, external presentations, liaison roles, webinars and roundtable meetings
- Support professional development of regulatory staff

OTAT Research Goals & Objectives

Goal 1: Chemistry, manufacturing, controls: Enhance quality, consistency, and performance of advanced therapeutics through development of strategies and methods for improved raw materials sourcing, manufacturing as well as product characterization, including test methods, standards, identification of Critical Quality Attributes, and pursuit of related biological investigations.

Objectives:

- Identify product attributes that are predictive of safety, effectiveness, and potency, plus attributes indicative of identity and stability.
- Develop and improve test methods used for product characterization to advance their sensitivity, specificity, and predictive value.
- Analyze existing and emerging strategies employed in design of advanced therapeutics and their manufacturing, and associated impact on structure, function, safety, and effectiveness.

Goal 2: Preclinical and clinical investigations: Enhance safety and effectiveness of advanced therapeutics through establishment of *in silico, in vitro and in vivo* preclinical models, and conduct of analyses to increase understanding of clinical trial design issues and patient characteristics that determine outcomes.

Objectives:

- Characterize preclinical models that relate specific product properties to biological performance and/or clinical outcomes.
- Analyze immune responses and their impact on product performance, and identify product or patient characteristics predictive of immunogenicity.

- Use preclinical models (in silico, in vitro, in vivo) to assess product and recipient issues, such as the potential for pathogen transmission and other adverse reactions.
- Analyze advanced therapeutics clinical trial issues including risk assessment, clinical trial design and monitoring, study of rare diseases, pediatric use, and donor safety.
- Conduct investigations on products implicated in adverse events post-licensure.

Goal 3: Safety issues related to human tissues: Enhance safety and effectiveness of donor screening tests, devices and technologies used in sourcing, manufacturing, processing, and/or testing of tissues and advanced therapeutics.

Objectives:

- Develop and characterize tests to identify donors suitable for donation of tissues, cells, and plasma proteins for therapeutic use.
- Evaluate methods and conditions for improved tissue processing.
- Develop and evaluate methods for better pathogen inactivation and pathogen detection in cell and tissue products.

OTAT Regulatory Portfolio

The products regulated by OTAT include gene therapies, cell therapies, plasma protein therapeutics, recombinant replacement proteins, therapeutic vaccines and advanced therapies for cancer, regenerative medicine products, xenotransplantation products, cord blood, tissue and tissue-based products, donor screening tests, and devices used in conjunction with these products.

Products Regulated by OTAT - Division of Plasma Proteins & Therapeutics

o Hemostatic Agents

- Thrombin (Bovine, Human & Recombinant)
- Fibrin Sealant and Fibrin Sealant Patch
- CryoSeal FS System

o Coagulation factors:

- Factors VIII and IX (Human plasma-derived & Recombinant)
- von Willebrand Factor (recombinant or as a factor VIII complex)
- Fibrinogen Concentrate
- Factor XIII
- Thrombin
- Prothrombin Complex Concentrate

o Anti-coagulants

- Protein C
- Antithrombin III (Human plasma-derived & Recombinant)
- Recombinant ADAMTS13

o General Immune globulins (IGIV, IGSC, IGIM) for PID, auto-immune disease (e.g. ITP), neurological diseases (e.g. CIDP)
o Specific Immune globulins enriched for particular antibody specificities (e.g. rabies, tetanus, hepatitis B, anthrax)
o Enzyme inhibitors for hereditary deficiencies (e.g. Alpha-1 Proteinase Inhibitor and C1 Esterase Inhibitor)
o Antivenins and antivenoms (snake, scorpion, spider)

o "Bypassing" Products

- Anti-Inhibitor Coagulation Complex (e.g., FEIBA)
- Recombinant activated Factor VII

Products Regulated by OTAT - Division of Cellular & Gene Therapies

- Stem cells/stem cell-derived
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
  - Functionally mature/differentiated (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- Gene therapies – Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)

- Cancer vaccines and immunotherapies
- Xenotransplantation products
- Devices and combination products
  - Engineered tissues/organs
  - Selection devices for the manufacture or delivery of cells

- Tissue- based products

Products Regulated by OTAT - Division of Human Tissues

- Tissue products

Public workshops with OTAT participation in planning and organizing

- **Annual US-Japan Cellular and Gene Therapy Conferences**
- September 20, 2017, titles "**Regulatory Expectations for Xenotransplantation Products**", Baltimore, MD
- Co-sponsored with NIST "**Cell Counting Workshop: Sharing practices in cell counting measurements**, April 10, 2017.

- Co-organized with OBE, OCOD, and stakeholders a public workshop on ***Identification and Characterization of the Infectious Disease Risks of Human Cells, Tissues, and Cellular and Tissue-based Products;*** February 8-9, 2017, College Park, MD
- **CASSS Bioassay Workshop. April 2016**
- **Nov 1 HRA/FDA Workshop on Gene Editing**
- **Organizer and Session chair:** PPTA/FDA/USP/EDQM Immunoglobulin Stakeholder Forum on ***Measurement Methods for Procoagulant Activity of Immunoglobulins***. September 2016 Rockville, MD
- **Session co-chair:** Blood Products Workshop on ***Gene Therapy Treatments for Hemophilia A & B*** at the CaSSS Well Characterized Biotechnology Pharmaceutical (WCBP), 21st Symposium on the Interface of Regulatory and Analytical Sciences for Biotechnology Health Products. January 2017 Washington, DC
- **Session co-chair:** Workshop "***Development Activities (Early and Late Phase), I Just Received Breakthrough, Now What Do I Do?***" at the CaSSS WCBP, 20th Symposium. January 2016 Washington, DC
- **Session co-chair:** Workshop "***Development Activities (Early and Late Phase), I Just Received Breakthrough, Now What Do I Do?***" at the CaSSS WCBP, 20th Symposium. January 2016 Washington, DC
- **Session co-chair:** Blood Products Workshop at the CaSSS WCBP, 18th Symposium. January 2014 Washington, DC
- Co-organizer of a section in 2016 Conference on ***Emerging Trends for Higher Order Structure Characterization in Biopharmaceutical Development*** (26-28 January 2016, Washington, DC).
- Organized an FDA public Workshop, ***New Methods to Predict the Immunogenicity of Therapeutic Coagulation Proteins***; September 17-18, 2015, Bethesda MD.
- Co-organized a Working Group with the National Heart, Lung, and Blood Institute (NHLBI), ***Toward the Rational Design of Optimally Functional Non-Immunogenic Factor VIII Therapeutics***; June 8-9, 2015, Bethesda, MD.

Anticipated products and developments (horizon scanning)

- Recombinant coagulation factors with improved properties
- Immune globulins protective against particular pathogens and from new sources, including transgenic animals
- Plasma protein therapeutics designed to minimize immunogenicity
- Gene therapy, cell therapy maturing; more late phase trials
- CAR T cells and cancer vaccines for cancer therapy
- Products involving genome editing of cells *in vitro* and *in vivo*
- Stem cell products
- Tissue engineered products

Office of Blood Research & Review

OBRR Mission

- Assure the safety, efficacy and availability of blood and blood components for transfusion and plasma for further manufacturing

- Assure the safety and effectiveness of HIV and other retroviral diagnostic tests

OBRR Activities

- Review, evaluate, and take appropriate actions on applications for investigational and commercial use of blood components, related drugs and devices, and devices for detection of transfusion transmissible pathogens
- Review, evaluate, and take appropriate actions on applications for investigational and commercial use of retroviral diagnostic tests
- Develop procedures and guidance governing review of OBRR regulated products
- Develop regulations and guidance governing practices of the blood industry related to blood donor eligibility and the manufacture and use of OBRR regulated products
- Establish physical standards to assure donor safety and the quality and safety of blood components, related products and retroviral diagnostic tests
- Perform establishment inspections and assist the Agency in regulatory compliance actions
- Perform health hazard evaluations and risk assessments of regulated products
- Engage in preparedness and response to address threats of emerging infectious agents (e.g. Ebola and Zika virus outbreaks)
- Outreach and cooperation to improve global public health where feasible
- Organize FDA Advisory Committee meetings and public scientific workshops on timely topics of significance to product regulation
- Conduct research to facilitate the development, manufacture, and regulatory evaluation of regulated products

OBRR Research Goals & Objectives

Goal 1: Assess and promote safety and effectiveness of transfusion products and related devices and technologies.

Objectives:

- Evaluation of ex vivo stored platelets and/ or red cells for a) safety and efficacy, b) toxicokinetics and development of biomarkers of product quality including Omics-based approaches and, c) microparticles-associated toxicities.
- Evaluation of the safety and effectiveness of oxygen carrying solutions, platelet-derived products and related biologics.
- Development and evaluation of reference panels for molecular typing methods for blood groups and HLA antigens.
- Facilitate development of pathogen reduction technologies applicable to Whole Blood and blood components.

Goal 2: Assess and promote safety and effectiveness of Transfusion-Transmitted Infectious Disease (TTID) agent donor screening and supplemental tests and retroviral diagnostics.

Objectives:

- Evaluation of screening and confirmatory technologies for detection of TTID agents for assurance and enhancement of blood safety.
- Development and evaluation of reference panels for screening and confirmatory tests for TTID agents and retroviral diagnostics.

- Facilitate preparedness for blood safety from emerging infectious agents and other pathogens of global significance through investigations of mechanisms of transmission and pathogenesis.

OBRR Regulatory Portfolio

- Blood and blood components for transfusion
- Plasma for further manufacturing use (including fractionation to make injectable plasma derivatives)
- Devices used in manufacture of blood and blood components (e.g., Blood Establishment Computer Software, automated cell separators, blood grouping and cross-matching reagents and devices, HLA tests)
- Blood collection containers and additive solutions (e.g., anticoagulants)
- Plasma volume expanders (albumin, dextrans, hetastarches)
- Oxygen carrying solutions (HBOCs, perfluorocarbons)
- Donor screening tests and confirmatory tests for transfusion-transmissible infections; pathogen reduction devices
- Diagnostic tests for human retroviruses

Office of Vaccines Research & Review

OVRR Mission Statement

Protect and enhance the public health by assuring the availability of safe and effective vaccines, allergenic extracts, and other related products.

OVRR Activities

- Review, evaluate, and take appropriate actions on INDs, BLAs, amendments and supplements to these applications for vaccines and related products, conducting inspections, etc.
- Develop policies and procedures governing the pre-market review of regulated products
- Conducting research related to the development, manufacture, and evaluation of vaccines and related products

OVRR Research Goals & Objectives

Goal 1: Enhance the safety of preventive vaccines and related biological products through the development of models, methods and reagents needed in the manufacture and evaluation of these products.

Objectives:

- To develop methods, assays and standards ensuring the purity of vaccines and related biological products
- To evaluate the utility of novel scientific technologies to assess and maintain the quality and consistency of vaccines and related biological products
- To develop new approaches to study potential toxicity of product components, including adjuvants
- To determine and study biomarkers of pathogenicity and develop methods to evaluate the safety of live vaccines
- To investigate the mechanism of vaccine-related adverse events and approaches to prevent and mitigate them.

Goal 2: Improve the effectiveness of vaccines and related biological products through the development of models, methods and reagents needed to measure and predict the effectiveness of these products.

Objectives:

- To study and develop methods to assess the potency of vaccines and related products.
- To study disease pathogenesis and identify correlates of protection and biomarkers to predict effectiveness of vaccines and related products.
- To study the mechanisms of innate and adaptive immunity against viral and bacterial diseases and mechanisms of immunopathology, including allergy.
- To develop new approaches to enhance the immunogenicity, potency, and protective effects of vaccines and related biological products.
- To identify mechanism of action of adjuvants and methods for predicting their added benefit.

Goal 3: To develop and study approaches to enhance the availability of vaccines and related biological products.

Objectives:

- To create new approaches to inducing protective immunity, modifications of antigen presentation and vaccine delivery routes.
- To create and evaluate methods for controlling the manufacturing process.
- To assess the utility of novel vaccine manufacturing platforms.
- To develop science-based approaches to the regulation of novel products such as live biotherapeutic and human microbiota-based products.
- To create methods for evaluation of vaccines and related biological products that lead to refinement, reduction, and replacement of tests in laboratory animals (3R).

OVRR Regulatory Portfolio

- Bacterial vaccines (inactivated)
- Bacterial vaccines (live attenuated)
- Viral vaccines (inactivated)
- Viral vaccines (live attenuated)
- Combination products (inactivated)
- Allergenic extracts (diagnostic and therapeutic) >2,000
- Live biotherapeutic products

Appendix 7. Teleconferences and Site Visit Agendas

AGENDA
CBER Research Program Review – CBER Overview
Teleconference 1
March 31, 2017

2:00 pm – 2:05 pm	Introductions/Roll Call
2:05 pm – 2:10 pm	Purpose, Goal, Charge & Timeline

2:15 pm – 2:25 pm	Questions from the Subcommittee
2:25 pm – 2:45 pm	CBER Regulatory Portfolio, Strategic Goals & Research Program Overview
2:45 pm – 3:00 pm	Questions from the Subcommittee
3:00 pm	Adjourn

AGENDA
CBER Research Program Review – CBER Overview
Teleconference 2
April 7, 2017

3:00 pm – 3:05 pm	Roll Call
3:05 pm – 3:15 pm	T-con 1 Questions from the Subcommittee
3:15 pm – 2:45 pm	Overview of CBER Research Management Career Pathways for Research Scientists Evaluation of Research Scientists Scientific Research Resources
2:45 pm – 3:00 pm	Questions from the Subcommittee
3:00 pm	Adjourn

AGENDA
CBER Research Program Review – OVRR Overview
Teleconference 3
April 10, 2017

11:00 pm – 11:05 am	Roll Call
11:05 am – 11:15 am	T-con 2 Questions from the Subcommittee

11:15 am – 11:45 am	Overview of Office of Vaccine Research & Review Marion F. Gruber, PhD Office Director Overview of Division of Bacterial, Parasitic and Allergenic Products Jay E. Slater, MD Overview of Division of Viral Products Jerry Weir, PhD
11:45 am – 11:00 am	Questions from the Subcommittee
12:00 pm	Adjourn

AGENDA
CBER Research Program Review – OTAT Overview
Teleconference 4
April 19, 2017

11:00 am – 11:05 am	Roll Call
11:05 am – 11:15 am	T-con 3 Questions from the Subcommittee
11:15 am – 11:45 am	Overview of Office of Tissues & Advanced Therapies Suzanne Epstein, PhD, Office Associate Director for Research Overview of Division of Plasma Protein Therapeutics Basil Golding, MD, Division Director Overview of Division of Cellular and Gene Therapies Raj K. Puri, MD, PhD, Division Director
11:45 am – 12:00 am	Questions from the Subcommittee
12:00 pm	Closed subcommittee discussion without CBER staff
12:30 pm	Adjourn

AGENDA
CBER Research Program Review – OBRR Overview
Teleconference 5
May 9, 2017

11:00 am – 11:05 am	Roll Call
11:05 am – 11:15 am	T-con 4 Questions from the Subcommittee

11:15 am – 11:45 am	Overview of Office of Blood Research & Review Jay S. Epstein, PhD, Director Overview of Division of Blood Components and Devices Orieji Illoh, MD, Division Director Overview of Division of Emerging & Transfusion Transmitted Diseases Hira Nakhasi, PhD, Division Director
11:45 am – 12:00 am	Questions from the Subcommittee
12:00 pm	Closed subcommittee discussion without CBER staff
12:30 pm	Adjourn

AGENDA
CBER Research Program Review – OBE Overview
Teleconference 6
May 23, 2017

2:00 pm – 2:05 pm	Roll Call & T-con 5 Questions from the Subcommittee
2:05 pm – 2:50 pm	Overview of Office of Biostatistics & Epidemiology Steven Anderson, PhD, Director Overview of Analytics & Benefit-Risk Assessment Research Program Richard Forshee, PhD, Associate Director for Research Overview of Division of Biostatistics John Scott, PhD, Division Director Overview of the High-Performance Integrated Virtual Environment Mark Walderhaug, PhD, Associate Office Director for Risk Assessment
2:50 pm – 3:00 pm	Questions from the Subcommittee
3:00 pm	Closed subcommittee discussion without CBER staff
3:30 pm	Adjourn

Food and Drug Administration
Center for Biologics Evaluation & Review (CBER)
Science Board Subcommittee (SBSC) Research of CBER Program Review

Site Visit
Tuesday, June 6, 2017

White Oak Building 31, Great Room, Salon C
10903 New Hampshire Avenue

Silver Spring, MD 20993

AGENDA

	Closed Briefing Session	Drs. Marks, Witten, Wilson and Science Board Subcommittee
8:00 a.m.	***Welcome and Introductions***	Dr. Barry Byrne, Science Board Subcommittee Chair
8:05 a.m.	***Opening Remarks***	Dr. Peter Marks
8:30 a.m.	***Office of Vaccines Research & Review***	
	Opening Remarks	Dr. Philip Krause, OVRR Deputy Director
	Scientific Presentations	
8:40 a.m.	***Facilitating the Introduction of New Vaccines: Addressing Potential Safety Concerns with Novel Cell Substrates*** Laboratory of DNA Viruses, Division of Viral Products	Dr. Keith Peden, Laboratory Chief
8:55 a.m.	Q&A	
9:00 a.m.	***Rational Design of Safe and Effective Vaccines*** Laboratory of Method Development, Division	Dr. Steven Rubin, Laboratory Chief
9:15 a.m.	of Viral Products	
9:20 a.m.	Q&A	
	Interactions between the immune system, the microbiome, and Clostridium difficile *Laboratory of Mucosal Pathogens & Cellular Immunology,* Division of Bacterial, Parasitic &	Dr. Paul Carlson, Principal Investigator
9:35 a.m.	Allergenic Products	Office Leadership, Research Staff & Science Board Subcommittee
9:40 a.m.	Q&A	
	Informal discussion	
9:50 a.m.	***Break***	
10:00 a.m.	***Office of Blood Research & Review***	
	Opening Remarks	Dr. Jay Epstein, OBRR Director

	Scientific Presentations	
10:05 a.m.	***Oxidative Toxicity of Hemoglobin-based Oxygen Therapeutics and the Design of Safer Products*** Laboratory of Biochemistry and Vascular Biology, *Division* of Blood Components & Devices	Dr. Abdu Alayash, Laboratory Chief
10:15 a.m.	Q&A	
10:20 a.m.	***Genomics and Proteomics-Based Assay Development for Detection of Babesia microti in Blood Donors*** Laboratory of Emerging Pathogens, Division of	Dr. Sanjai Kumar, Laboratory Chief
10:30 a.m.	Emerging & Transfusion Transmitted Diseases	
10:35 a.m.	Q&A	Office Leadership, Research Staff & Science Board Subcommittee
	Informal discussion	

11:00 a.m.	***Office Biostatistics & Epidemiology Opening Remarks***	Dr. Steven Anderson, OBE Director
	Scientific Presentations	
11:05 a.m.	***Benefit–Risk Assessment to Support Management of Transfusion-Transmission Risk of Infectious Diseases*** Computer Modeling and Simulation of Benefits-risks of Biological Products Division of	Dr. Hong Yang, Principal Investigator
11:15 a.m.	Biostatistics	
	Q&A	Dr. Taxiarchis Botsis, Principal Investigator
11:20 a.m.		
11:30 a.m.	***Medical Informatics for Post-market Safety Surveillance***	Office Leadership, Research Staff & Science Board Subcommittee
11:35 am.	Decision Support Environment, Division of Biostatistics	
	Q&A	

	Informal discussion (OBE)	
11:00 a.m.	***Office Biostatistics & Epidemiology Opening Remarks***	Dr. Steven Anderson, OBE Director
	Scientific Presentations	
11:05 a.m.	***Benefit–Risk Assessment to Support Management of Transfusion-Transmission Risk of Infectious Diseases*** Computer Modeling and Simulation of Benefits-risks of Biological Products Division of	Dr. Hong Yang, Principal Investigator
11:15 a.m.	Biostatistics	
	Q&A	
11:20 a.m.		Dr. Taxiarchis Botsis, Principal Investigator
11:30 a.m.	***Medical Informatics for Post-market Safety Surveillance***	
11:35 am.	Decision Support Environment, Division of Biostatistics	
	Q&A	Office Leadership, Research Staff & Science Board Subcommittee
	Informal discussion (OBE)	
12:00 p.m.	***Lunch-Executive Session Closed***	Science Board Subcommittee

12:45 p.m.	**Laboratory Tour**	
1:00 p.m.	***High Performance Integrated Virtual Environment*** Computational Sciences (OBE)	Dr. Vahan Simonyan (71/0158)
1:15 p.m.	***Improving the Safety of the Blood Supply by Developing Sensitive Diagnostic Tools*** Laboratory of Molecular Virology (OBRR)	Dr. Indira Hewlett (52/72/4230)
1:30 p.m.	***Investigating the Effects of Cell-materials Interactions on the Safety & Effectiveness of Cell-based Products***	Dr. Kyung Sung (52/72/3248)
1:45 p.m.	Cellular and Tissue Therapy Branch (OTAT)	
	Understanding Norovirus Diversity & Immune Responses to Inform Vaccine Design Laboratory of Hepatitis Viruses (OVRR)	Dr. Gabriel Parra (52/72/1376)

2:00 p.m.	***Office of Tissues & Advanced Therapies Opening Remarks***	Dr. Wilson Bryan, OTAT Director
	Scientific Presentations	
2:05 p.m.	***Synonymous Mutations: Relevance to Disease, and Protein Therapeutics (Dr. Chava Kimchi-Sarfaty, Principal Investigator)***	*Dr. Basil Golding, Division Director*
2:25 p.m.	***Structural Dynamics for Antibody-Mediated Neutralization (Dr. Pei Zhang, Principal Investigator)*** Hemostasis *Branch* Division of Plasma Protein Therapeutics	
2:30 p.m.	Q&A	

		Dr. Steven Bauer, Branch Chief
2:40 p.m. 2:45 p.m.	***Strategies to Improve Characterization of Stem-Cell Based Cellular Products*** *Cellular & Tissue Therapy Branch, Division of Cellular & Gene Therapies*	
2:55 p.m.	Q&A	
		Dr. Andrew Byrnes, Branch Chief
3:00 p.m.	***Improving animal models for adenovirus gene therapies*** *Gene Transfer & Immunogenicity Branch, Division of Cellular & Gene Therapies*	
	Q&A	
		Office Leadership, Research Staff & Science Board Subcommittee
	Informal discussion	
3:20 p.m.	***Break***	
3:30 p.m.	***Closed Executive Session***	Science Board Subcommittee
5:00 p.m.	***Closed Summary Briefing Session***	Drs. Byrne, Monto, Marks, Witten, and Wilson
5:30 p.m.	***Adjournment***	