Introduction and Overview of the Center for Biologics Evaluation and Research (CBER)

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Welcome. I'm Peter Marks, the Director of the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research or "CBER." I'd like to introduce to you a web-based program that is intended to provide information on the work we do at CBER in our oversight of biological products in the United States. The program that follows had its origins in a live program held with a group of foreign regulatory counterparts several years ago. This web-based production was developed in order to extend our outreach to those foreign regulators who are unable to participate in live events. Since these are recorded sessions, I need to point out to viewers that the presentations represent a snapshot in time. Given the advancing science and regulatory environment, the presentations will become dated over time. We hope to refresh the program to keep pace with any changes to policy, regulations or legislation that will undoubtedly occur in the future. I very much hope that you will find this program useful. Thank you for taking the time to learn more about our Center.

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In thinking about what you would be most interested in hearing about in this introduction and overview, I put together a presentation that provides information on what the Center does for both product development and public health both in the United States and globally. First, I would like to tell you a bit about our history and mission and the products that we regulate, then go on to explain the significance of complex biologic products, review why these products and the processes used to produce them are intertwined, discuss the relevance of applied scientific research to complex biologics, provide a more detailed example of a cutting-edge biologic, and review the Center's efforts to facilitate product development.

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The origins of the Center for Biologics Evaluation and Research predate the formation of the U.S. Food and Drug Administration. Around the turn of the nineteenth to twentieth centuries two of the most important medical products were biologics: smallpox vaccine and diphtheria antitoxin. After two incidents in which contaminated smallpox vaccine and diphtheria antitoxin led to the deaths of 22 children, the precursor to the center came into being when Congress enacted the Biologics Control Act of 1902. Subsequently, that entity became part of the National Institutes of Health, and, in 1972, was moved to FDA as the Bureau of Biologics. In 1987, FDA's Center for Biologics Evaluation and Research was formed. Today, the Center has about 1200 full-time employees and its activities are consolidated at the FDA White Oak Campus in Silver Spring, Maryland.

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The mission of the Center for Biologics Evaluation and Research is to ensure the safety, purity, potency, and effectiveness of biological products. Some of our strategic goals are

shown here. Through its regulatory work and its applied scientific research, the Center facilitates the availability of safe and effective biological products. CBER also plays an important role in maintaining U.S. preparedness to address threats to the public health that arise as a result of terrorism, pandemic influenza and other emerging infectious diseases. In addition, a Center goal is to advance applied scientific research. Finally, CBER strives to improve global public health through international collaboration, including through research and information sharing.

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Now, turning to our products. Biologics, such as the vial of diphtheria antitoxin from the 1890's shown on the left, were among the earliest medical products to be regulated in the United States. Biologics now also include some of the most complex and cutting-edge products, such as those incorporating use of the CRISPR/Cas9 genome editing technology depicted on the right, which have great potential to positively impact medicine.

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Our Center regulates a variety of medical products that have in common complexity in their manufacturing and mechanism of action. These products include vaccines, including those for therapeutic purposes as well as for prevention of disease, allergenic products, live biotherapeutic products, such as probiotics and fecal microbiota transplants; blood and blood components, as well as devices for the preparation, testing, and storage of blood and tissues. We also regulate human tissues and cellular products, xenotransplantation products, and gene therapies. Our Center does not regulate most biologic proteins, such as monoclonal antibodies and protein hormones. These are regulated by the Center for Drug Evaluation and Research.

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So what is the significance of our Center's complex biologic products?

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Facilitating the availability of safe and effective vaccines to prevent disease is a key part of what we do. Here, you see a list of various infectious diseases, on the left with their incidence in the 1900's, before the introduction of vaccines, and on the right with their incidence in 2013. Cases of measles (among other diseases) have been remarkably reduced and now essentially just reflect disease that is imported into the United States. Smallpox and diphtheria have been eliminated entirely. Vaccines clearly represent one of the most effective public health interventions of the twentieth century. And the success of vaccines depends on their use by the population, which in turn depends in large part on people's confidence in their safety and effectiveness. Vaccines had a tremendous positive impact on public health in the twentieth century and, because of emerging infectious diseases, they remain incredibly important for public health today. Over just the past few years we have seen the emergence of Ebola virus, Zika virus, and H7N9 influenza, and there will undoubtedly be others in the future. Being able to rapidly develop safe and effective vaccines is a public health imperative.

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Ensuring the safety of the blood supply is another important part of what we do. Existing and emergent infectious diseases can also have an adverse effect on the safety of blood products for transfusion, as was dramatically illustrated in the early 1980's by the human immunodeficiency virus, or HIV, epidemic. At that time the risk of HIV associated with transfusion of a unit of blood was as high as 1 in a hundred in some places in the United States. We have worked together with regulated industry to facilitate the introduction of testing that has dramatically reduced the risk of HIV, hepatitis B, and hepatitis C in the blood supply, and we continue to work to keep the blood supply safe from emerging threats like West Nile virus and Zika virus.

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In addition to well-established products like vaccines and blood products, the Center is responsible for a number of advanced therapies at the leading edge of medical science, such as ex vivo and in vivo gene therapy. Using ex vivo gene therapy, cells are isolated from an individual and then transfected with a gene therapy construct in a laboratory prior to their growth and reinfusion into that individual. In contrast, using in vivo gene therapy, the genetic material is directly administered to an individual intravenously or by another route, ultimately resulting in cellular modification. In either case, the repair, replacement, or introduction of new genes has the potential to address many different diseases that are currently without effective treatment.

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Finally, regenerative medicine is a field with great promise that goes directly to the FDA's role in helping to meet unmet medical needs. Regenerative medicine products that the Center handles include cell therapies, therapeutic tissue engineering products, human cell and tissue products, and some combination products involving cells and devices such as scaffolds that the cells can grow on. I will focus more on regenerative medicine a bit later on in my talk.

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A defining feature of many complex biologic products is that the product and the process used to produce it are intimately intertwined. If the process is not well-defined and controlled, there may be inconsistency in the product, which may cause those products to have different effects or even to be unsafe. A product with a reproducible safety and efficacy profile is invariably associated with a product manufactured by a process that is well-controlled.

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Just to give an example of how manufacturing process and product are intertwined: our Center does regulate the subset of therapeutic proteins that are involved in blood coagulation, whether they are purified from blood, made in cell culture, or administered as a gene therapy. Factor VIII is a large protein with sugar molecules attached to it that circulates in the blood and is involved in blood clotting, and hemophilia A is the serious bleeding disorder resulting from inadequate or absent amounts of factor VIII in the blood. In the 1920's and 1930's it was realized that blood transfusion could be used to

treat bleeding episodes. Subsequently, it was found that the necessary factor was present in fresh frozen plasma and then in a derivative of fresh frozen plasma called cryoprecipitate. As the underlying science identified the properties of factor VIII, it was purified from plasma. Ultimately, the gene was cloned, allowing factor VIII to be produced in, and purified from, cell culture. In the future, the thorough understanding of the structure and function of the protein that we now have may make treatment of hemophilia possible through administration of a gene therapy product. So, to summarize, a constant feature in the evolution of products for the treatment of hemophilia A has been the intimate connection among these complex products, the underlying science, and the production processes.

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In addition to complexity in manufacturing, many of the biologics handled by our Center have complex mechanisms of action. Understanding the mechanism of action of biologic products can facilitate the development or improvement of these products, and can also assist in regulatory evaluation. These are just some of the reasons why our Center conducts applied scientific research, which is also sometimes called regulatory science. In the next few slides, I will provide you with examples of applied research from each of the four offices in our Center involved in its conduct.

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An example of vaccine research involves looking into the reasons for the recent resurgence in whooping cough, which is caused by Bordetella pertussis, despite the availability of a vaccine that was found to be safe and effective. Scientists at our Center developed a baboon model for this disease to better understand what was going on.

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The baboon model suggested the mechanism of vaccine failure. CBER researchers compared an older generation of whole cell pertussis vaccine, which is no longer given in the United States, to the current generation of acellular pertussis vaccine, which is associated with fewer side effects at the time of administration. Both vaccines were found to produce robust antibody responses, but the cellular immune responses were different. It turns out that the clearance of the bacteria from the body is much more rapid in those vaccinated with the whole cell vaccine than in those vaccinated with the acellular vaccine. This means that the newer acellular vaccine does not rapidly eliminate the bacteria from the body, and therefore allows the disease-causing bacteria to be transmitted to unvaccinated contacts. The implication here is that further work is needed on the pertussis vaccine to retain the efficacy of the older whole cell vaccine while maintaining the benefit of fewer reactions that is associated with the newer acellular vaccine.

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Let's look at the area of blood research. For a number of years, it had been known that the use of immune globulin products was associated with different thrombotic serious adverse events such as myocardial infarctions, stroke, and venous thromboembolism. The causes of these adverse events were not clear. A few years ago, during a cluster

of cases associated with specific lots of immune globulin products, our researchers examined whether an activated clotting factor, factor XIa, could be the cause.

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In order to identify and address the cause of thrombotic events, the researchers looked at the effect of adding factor XIa to different immune globulin products that were not associated with increased risk of thrombosis. The graph on this slide shows that the addition of dilutions of the factor Xia, in blue, mirrored the addition of dilutions of the lot of immune globulin that was associated with thromboembolic events. Additional scientific work was conducted to confirm this association and resulted in the development of a reference standard reagent and a laboratory assay for contaminating factor XIa. The assay and reagents were widely shared with industry, resulting in improved safety of the entire product class.

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Cell, tissue, and gene therapy research is at a somewhat earlier stage than some other medical products regulated by CBER. Identifying the best methods and characteristics to assure safe and effective cellular therapies is still evolving. This is particularly the case for stem cells taken from an individual. The parameters that define how certain stem cells that are given to an individual will ultimately perform in terms of safety and efficacy are not yet well-defined. Our investigators have taken a multidisciplinary approach using molecular genetics and cell biology to try to help elucidate the relevant parameters.

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One method applied by CBER scientists was to use automated microscopy-based quantification to look at the ability of different stem cell lines to differentiate along a given lineage. They found that the mesenchymal stem cell lines taken from different individuals were different from one another in their ability to differentiate. In addition, these differences changed over the course of time through passage in cell culture and the differences observed were inconsistent. Understanding that such differences can occur and need to be characterized to the extent possible, is a finding that has been important to communicate to those developing stem cell products.

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Our applied scientific work is not just confined to the laboratory. The Center also conducts biostatistics and epidemiology research. As you may be aware, FDA has been using real world evidence in the evaluation of product safety for a number of years, using large healthcare database systems such as Sentinel and Healthcore. Rigorous methodology has been developed to facilitate signal identification and confirmation in order to investigate safety signals. In addition, researchers are investigating the ability of real world evidence to inform evaluations of effectiveness.

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Our investigators have provided an example of how real world evidence might contribute to the determination of effectiveness by comparing the effectiveness of high-

dose and standard-dose influenza vaccine using the Medicare Database. By looking at the outcomes in close to a million recipients of high-dose influenza vaccine and comparing them to over a million and a half recipients of standard-dose vaccine, they found that the high-dose vaccine was more effective for the prevention of probable influenza infections. This real world evidence agreed well with the outcome of a previously conducted Phase III trial that involved almost 32,000 individuals. Thus, real world evidence shows promise in certain settings to help facilitate product development.

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To summarize, regulatory science plays an important role at CBER, helping us to pursue our regulatory mission and facilitate product development. Such research ensures the availability of scientific experts who understand the regulatory process, can proactively address regulatory science gaps, and can help respond effectively to public health emergencies.

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To put together what I have told you about complex biologic products at the cutting edge of science and medicine, I would like to briefly provide you with a more concrete example.

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Recently, chimeric antigen receptor-T cells have made the news in both the scientific and lay press because of their potential to meet unmet medical needs.

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Known as CAR-T cells for short, these products represent an ex vivo cell-based gene therapy potentially applicable to the treatment of hematologic malignancies, solid tumors, and infectious and autoimmune diseases. The products offer the possibility of providing therapeutic benefit with an extended duration of effect that may, in certain circumstances, be curative.

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CAR-T cells represent an improvement upon unmodified ex vivo expanded T cells targeting tumor antigens, which show some efficacy, but poor persistence. Instead, these genetically modified T cells harness immunity to attack tumor or other immune effector cells. The gene transfer improves the functional properties of the T cells that are genetically modified, for example by providing them with the ability to specifically recognize a certain category of target cells.

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Here is a diagram that provides a general overview of how CAR-T cell therapy works. Using a process called apheresis, white blood cells are obtained from an individual, T cells are isolated, and the gene transfer vector is used to introduce the genetic modification. The cells are then expanded to greater numbers in culture, formulated and tested, and then administered to the patient, usually after some type of pretreatment. The individual is then followed closely to address any side effects of the treatment.

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The chimeric antigen receptor introduced into the T cells is the key aspect of the therapy. Using molecular genetics, novel protein receptors can be created that combine features of different proteins into a new protein. This allows one to both target and activate T cells to eliminate a cancerous or undesirable cell type. In the figure on the right you see a diagram of the chimeric construct showing how an antibody head has been linked to parts of the T cell receptor. When the antibody binds its target on a cancer cell, it activates the T cell that contains the receptor to kill the cancer cell.

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Such genetically-modified cellular therapies have a number of potential advantages. Appropriate methods can be used to address the issue of location of genomic integration, and use of cutting-edge technology such as genome editing with CRISPR/Cas9 is possible. The technology allows the selection of appropriately transduced cells for administration to recipients, and the nature and extent of genetic modification of the cells can even be confirmed using next generation sequencing. Additionally, the effect of the cells can be prevented from getting out of control through the use of approaches such as the introduction of suicide genes into the cells that can be activated if need be.

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There are some potential challenges, however, to the use of these genetically-modified cellular therapies. These include the ability to consistently manufacture and characterize the cells, as well as the logistics of facilitating the harvest, production, and delivery of the cells. We also know that the administration of these cells may be associated with various short-term side effects, most notably a type of acute inflammatory process called cytokine release syndrome. All that being said, chimeric antigen receptor-T cells have already shown great promise in treating certain relapsed and refractory blood cancers, like childhood acute lymphoid leukemia and diffuse large B cell non-Hodgkin lymphomas.

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If fact, as of late 2017, there are two licensed CAR-T cell products in the United States. One of these, Kymriah, is for the treatment of appropriate pediatric and young adult patients with relapsed or refractory acute lymphoblastic leukemia and was associated with a complete response in about four out of five individuals treated. Another, Yescarta, is for the treatment of appropriate adults with relapsed or refractory large B-cell lymphoma, and it was associated with a complete response in about half of the individuals treated. And although the treatments have to be administered carefully, they represent a new treatment paradigm that may well lead to cures that were not previously possible. These are just two examples at the leading edge of what looks to be a transformational period in medical therapy for certain diseases.

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Finally, I want to touch upon how we try to put everything we do together to facilitate the development of complex biologics in the context of existing and recently enacted regulatory provisions.

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Over the past 25 years, the United States Congress has added increased flexibility to FDA's regulatory approach for drugs, including biologics, that treat serious conditions. Expedited development pathways include Fast Track designation, breakthrough designation, accelerated approval, and priority review.

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The latest Congressional action to help facilitate the development of medical products is the 21st Century Cures Act, which was signed into law on December 13th, 2016. This important Act has the goal of further speeding the discovery, development, and delivery of medical products to prevent and cure disease and improve health. The Act has a number of provisions relevant to FDA including: Patient-focused drug development, Advancing New Drug Therapies, Modern Trial Design and Evidence Development, Patient Access to Therapies and Information, Antimicrobial Innovation and Stewardship, Medical Device Innovations, and Improving Scientific Expertise and Outreach at FDA. Particularly relevant for the Center for Biologics Evaluation and Research are the Regenerative Medicine Provisions, which established a new expedited pathway for development.

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The Regenerative Medicine Advanced Therapy, or RMAT, designation was created to expedite the development and review of certain regenerative medicine products. This designation potentially applies to certain cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products. I should note that we consider genetically modified cellular therapies and gene therapies producing durable effects to be eligible for the designation.

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For a product to be eligible for the RMAT designation, the product must be intended for serious or life-threatening conditions and preliminary evidence must indicate the potential for the therapy to address unmet medical needs. Following the submission of a request to FDA, sponsors will receive a response within 60 days. Designation provides sponsors with increased interactions with FDA and with eligibility, as appropriate, for priority review and accelerated approval.

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For a product designated for accelerated approval, the 21st Century Cures statute explicitly expanded the ways that post-approval requirements can be fulfilled. As appropriate, sponsors may submit clinical evidence, clinical studies, patient registries or other sources of real world evidence such as electronic health records; collect larger confirmatory datasets, as agreed upon with the Agency; or conduct post-approval

monitoring of all patients treated prior to approval of the therapy. As for Breakthrough Therapy designation, we believe that one of the most valuable aspects of this program is the opportunity for increased interaction between sponsors and the Agency. Irrespective of whether RMAT designation has been granted, CBER is trying to help facilitate development in the field of regenerative medicine, and welcomes the opportunity to interact early with product developers. In this regard, we are happy to entertain informational pre-pre-IND meeting requests for sponsors who have a product concept or early data and need information regarding further development pathways.

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So to conclude, the Center for Biologics Evaluation and Research's mission is to bring innovative safe and effective therapies as quickly as possible to the benefit of the people of the United States and to others around the world. I want to take this opportunity to acknowledge the remarkable work of all of our staff, who work together every day to protect and promote public health in the United States and globally.

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Thank you so much for taking the time to listen to this presentation today. I hope that you have found it informative.