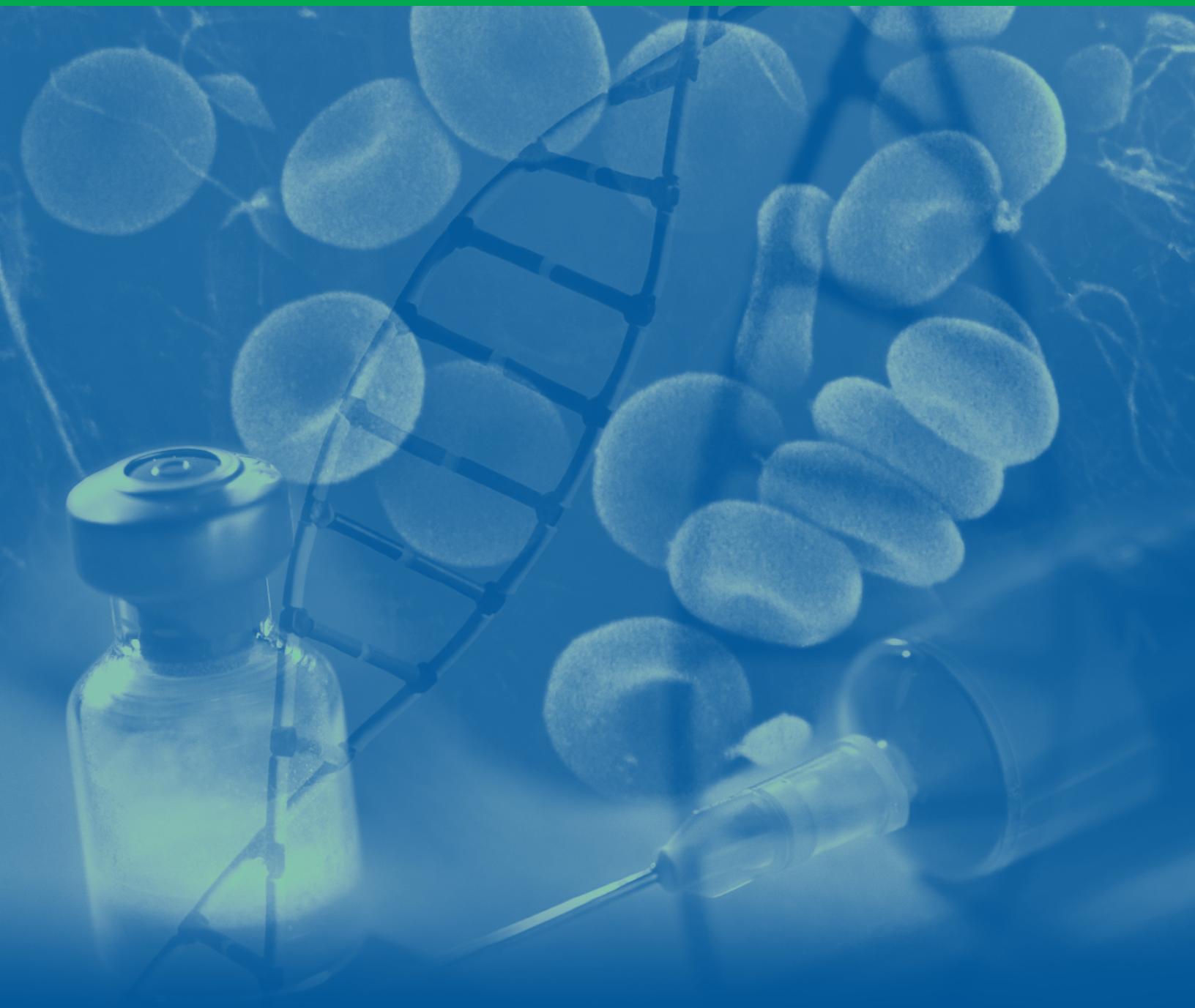
FY 2007 ANNUAL REPORT

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



Innovative Technology Advancing Public Health

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

Innovative Technology Advancing Public Health

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VISION AND MISSION

Vision

The Center for Biologics Evaluation and Research (CBER) uses sound science and regulatory expertise to:

- Protect and improve public and individual health in the United States (U.S.) and globally
- Facilitate the development of, approval of, and access to safe and effective products and promising new technologies; and
- Strengthen CBER as a pre-eminent regulatory organization for biologics

Mission

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

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

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

Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

A MESSAGE FROM THE DIRECTOR

August 2008

Dear Friends and Colleagues:

I am pleased to share with you the fiscal year (FY) 2007 Annual Report from the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA).

CBER works at the cutting edge of public health and science, regulating complex biological products that are essential to medicine and public health in the 21st Century. These products, which include vaccines, allergenics, blood and blood products, and cellular, tissue and gene therapies promise to revolutionize U.S. and global medicine and public health. Therefore, all of us have a significant stake in their safety, effectiveness and availability. CBER approaches these expectations with intense dedication and commitment.

FY 2007's annual report summarizes key accomplishments of an eventful and productive year. I share with the entire staff of CBER great pride in the work we've done in the fields of medicine, public health, regulatory science, and preparedness for emerging threats, as summarized below.

New products to protect and promote public health: We met or exceeded all of our review goals, including those under the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFMA), evaluating and approving new products that are already making critical contributions to the protection and promotion of health. These include new tests and reagents to help keep blood and plasma transfusions safe, new recombinant and plasma products to prevent bleeding, new vaccines against infectious diseases of global importance--including rotavirus and influenza, and extended indications for certain vaccines against influenza and meningitis.

In addition, we worked closely with the scientific community to help meet the unique challenges posed by cutting edge innovations, like cell and gene therapies, stem cells, and tissue engineering, which present both incredible promise, but also unique and novel challenges. For example, we co-sponsored tissue engineering workshops with the National Institute of Standards and Technology and other agencies, leveraged the expertise of our advisory committees and of product developers to help provide needed scientific insights and pathways for development of cell therapies, and established a joint CBER/Center for Devices and Radiological Health (CDRH) Tissue Engineered Products Review Team.

Global challenges and opportunities: Today, innovation, manufacturing, and regulation are all global, as are disease threats and their potential solutions. CBER is fully committed at the international level. As a recently re-designated World Health Organization (WHO) Collaborating Center for Biological Standardization, we help set and provide the standards needed to assure that a multitude of important

products are high quality, safe, and available. We work closely with sister regulatory and public health agencies to share information, particularly about product safety and manufacturing, and to proactively address public health threats; for example, initiating a collaborative global effort to develop standards for pandemic influenza vaccines. We strongly support efforts to harmonize product development and regulation.

We are engaged, through our Global Vaccine Initiative, in the effort to facilitate the development, evaluation, and availability of products to prevent or control diseases of global importance, from tuberculosis (TB), malaria, human immunodeficiency virus (HIV), and respiratory diseases to potential bioterrorism threats. We provide consultative assistance to product developers for vaccines to address such threats and engage with WHO and other partners to help strengthen global regulatory and scientific infrastructure, including in less developed regions of the world, so that such countries can successfully partner in identifying and meeting their own public health needs. Infectious diseases know no boundaries and we support these and other efforts to enhance global public health because they benefit and help protect everyone, including enhancing our nation's preparedness.

Public health and emerging threat preparedness: With the support of Congress, we have worked to strengthen the development and availability of products, and the infrastructure needed to protect the health of our citizens.

In the last year we licensed the first vaccine for protection against the H5N1 pandemic influenza threat and are interacting intensively with governmental partners and industry in numerous efforts to develop additional needed products (for example, cell culture, adjuvanted and recombinant vaccines). We believe these efforts will also bear fruit in improving seasonal influenza vaccines, as well as the scientific base and infrastructure for other infectious diseases prevention and control measures. Increasing the diversity and supply of seasonal influenza vaccine has been a major priority for us, and a gratifying and successful effort. Working collaboratively over the past three years, we helped double the number of U.S. licensed manufacturers and the supply of influenza vaccine to a record 134 million doses in 2007. This will prevent thousands of hospitalizations and deaths annually, and supports a U.S. and global infrastructure critical to public health. We also approved a new smallpox vaccine, produced using modern cell culture methods, which is now available in the Strategic National Stockpile in the event it is ever needed.

Finally, we continue work to anticipate and prevent threats to blood and tissue safety (such as malaria and mad cow disease) and availability (such as impacts of a pandemic) by facilitating the development of needed testing and providing guidance. As a result of these efforts, which include close collaboration with our stakeholders, our nation's blood supply is the safest it has ever been.

To help ensure such products continue to be safe, available, and high quality, we initiated new, centrally-managed, quality-assured product testing laboratories, and are developing better, faster testing methods that can be used by regulatory agencies and industry to test products that would be needed during a pandemic or to respond to other urgent needs. Moreover, we have bolstered our information technology (IT) and communications capacity to support mission-critical functions in such emergencies. These efforts have taken an "all can help us meet the diverse scientific and public health challenges" approach that we will surely face in the future.

Innovative Approaches to Product Safety: CBER emphasizes a life-cycle, multidisciplinary team approach to its product safety efforts, beginning with review plans for production and development, extending through the approval process, and continuing after products are marketed. Review teams include laboratory, clinical, safety and manufacturing scientists, who identify and evaluate potential safety concerns during product development, and design monitoring plans for products that are approved. Recent additional innovations include multidisciplinary safety teams, which include communications and emergency response experts that meet regularly to consider emerging safety issues for marketed vaccines, blood and tissues. These teams bring together and analyze data from such sources as adverse event reports,

manufacturing inspections, and product testing, acting on and communicating safety concerns promptly to the public and other stakeholders. In many of these efforts, we interact routinely and productively with the Centers for Disease Control and Prevention (CDC); leveraging and enriching each others' resources and expertise.

We also strongly support safety research that extends from basic science to enhance product quality, to innovative approaches for monitoring large healthcare and claims databases used to identify and/or analyze potential problems earlier. These accomplishments include successful development of methods and pilot studies utilizing Center for Medicare and Medicaid Services data to rapidly detect adverse events, as well as the creation of a dedicated unit to work with large data sets, and to better understand both their power and their limitations. These approaches have been recognized and are being more broadly applied, for example, in the FDA Sentinel Initiative, and in response to mandates of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to develop product safety surveillance using healthcare data.

Strong Science and Human Resources: We strive to base all of our activities and decisions on the best available information. Therefore, scientific excellence, our management processes, and the quality of our staff are critical to us. We initiated a new 360-degree assessment and coaching program to support development of our managers, and have funded a professional development budget that now enables all CBER employees to attend professional meetings or courses. We support continuing clinical activity for our Medical Officers and created new types of positions that combine review expertise with either policy work or informatics. These new positions are designed to help ensure the integration of product review with scientific input and expertise as we develop new regulatory policies and bioinformatics tools. In addition, our Research Management Program, which includes population sciences research, has made tremendous progress in helping to ensure that our limited resources are used productively and collaboratively, that they target public health and regulatory priorities, and that they benefit from public input and our advisory committees.

Our accomplishments and the overall contribution of CBER science to FDA's mission and to public health were positively recognized by the FDA Science Board in its recent evaluation of science at FDA, which noted that: "CBER has a rigorous process for establishing priorities and the impact of Center research on regulation. In addition, the leadership of CBER insists upon integration of laboratory scientists both in the review and manufacturing site inspection processes. External peer review of research programs is the norm rather than the exception."

FY 2007 was an exciting and productive one and we appreciate the essential input, collaboration, support and ideas we received from our stakeholders, including the public. I want to explicitly thank all of you for your contributions. I am proud and excited about what we have accomplished and can continue to accomplish working together.

We appreciate the trust placed in us as we work to fulfill our mission to protect and improve health in the U.S. and globally.

Jesse L. Goodman, M.D., M.P.H.
Director
Center for Biologics Evaluation and Research

OUR PRODUCTS

Blood and Blood Products[1-9]

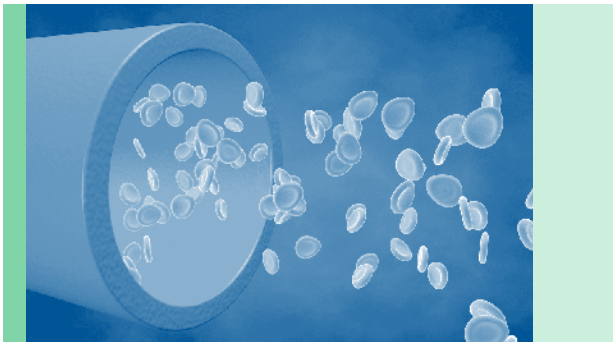
FDA is responsible for ensuring the safety of the nation's blood supply by minimizing the risk of infectious disease transmission and other hazards, while helping to ensure there is an adequate supply of blood and blood products.

CBER plays the lead role in this critical oversight of blood and blood products through several key activities:

- Regulating blood and blood components that are used for transfusion and for the manufacture of products
- Regulating blood products, such as clotting factors, concentrates, immune globulins and albumin
- Establishing reference standards and performing lot release testing
- Regulating devices including those used to prepare blood and blood components; blood-establishment computer software (BECS), cell separators, and blood collection containers
- Regulating tests that screen blood donors for human immunodeficiency virus-type 1 (HIV-1), hepatitis B virus (HBV), hepatitis C virus (HCV), West Nile virus (WNV), human T-lymphotropic virus types I and II (HTLV-I/II), as well as the syphilis spirochete
- Monitoring, analyzing, and acting on reports of biological product deviations and adverse clinical experiences.

CBER encouraged development of highly sensitive nucleic acid tests (NATs) for the detection of HIV-1 and HCV. These tests are now FDA-approved and recommended for use in screening blood donors to reduce the risk of transmission of these infectious agents. To standardize the performance of these tests, CBER developed essential lot release reagents.

CBER licensed the first WNV blood screening assay in 2005 and a second blood screening assay in 2007. The implementation of investigational screening assays in 2003, followed by licensed assays, has identified more than 2,500 potentially infectious donations, representing between 2,500 and 7,500 transfusable



blood components. This screening has likely prevented thousands of potentially serious or fatal infections during the last 5 years.

Over a period of years, FDA has progressively strengthened the overlapping safeguards that protect patients from unsafe blood and blood products. For example, over the past decade, CBER has worked actively with the blood community to redesign, streamline, and cognitively assess a standardized donor screening questionnaire. This questionnaire is now in broad use throughout the U.S. for screening blood donors. Blood donors are asked specific questions about their medical and behavioral history and given educational materials about risk factors specific for infection with a transmissible disease. This upfront donor screening helps to identify potential donors at high risk for having a transmissible infection; and thus enables blood banks to defer potentially high-risk donors prior to testing. This deferral strategy is especially important in the absence of donor screening tests for infectious diseases transmitted through donated blood.

To further enhance blood safety, FDA requires blood establishments to maintain lists of donors considered unsuitable to donate blood based on test results or identified risk factors for infectious diseases that can be transmitted by blood. These facilities are also required to quarantine donated blood until they determine the blood is suitable for release. In addition, FDA has continued its oversight through inspections of blood collection and manufacturing facilities.

Vaccines[10-21]

Vaccines, products regulated by CBER, have made significant contributions to medicine during the 20th century, and are likely to continue to change the medical landscape in the 21st century even more as advances in biotechnology increase. Many of these products are pediatric vaccines that have contributed to the dramatic reduction or elimination of life-threatening childhood diseases in the U.S. (e.g., diphtheria, measles, and polio).

CBER plays an important role in the development of these products, starting early in the process and continuing throughout their market life. We have optimized the vaccine development, review, and licensing process to encourage and expedite development of new vaccines to further the public health. In addition, CBER's own research program plays a role in vaccine development in a number of ways, such as developing animal models that might predict vaccine effectiveness and, in the case of influenza vaccines, developing new potency assays, and preparing antisera to be used in potency testing of these vaccines. Our research program also studies the genetic makeup of reference influenza viruses to determine their potential to grow easily in either eggs or cell cultures, a characteristic important in increasing manufacturing yield for influenza vaccines. CBER has also developed tests to assess the tumor-forming potential of cell cultures that may be used to manufacture vaccines; and that can screen for contaminating infectious agents in these cultures.

This past year, CBER approved the first pandemic influenza vaccine against H5N1 influenza virus and two new vaccines against seasonal influenza. We also approved an expansion of the age group for the live attenuated influenza vaccine, Flumist, down to 2 years of age. These efforts to encourage the entry of additional influenza vaccine manufacturers into the market have resulted in the doubling of licensed influenza manufacturers from 3 to 6 in the past 3 years and the production of the largest number of influenza vaccine doses ever. CBER also approved a new smallpox vaccine this past year. In addition, there are vaccines under development that offer the promise of preventing other serious infectious diseases (e.g., pandemic influenza, tuberculosis, HIV-1, and malaria).

Cellular and Gene Therapies

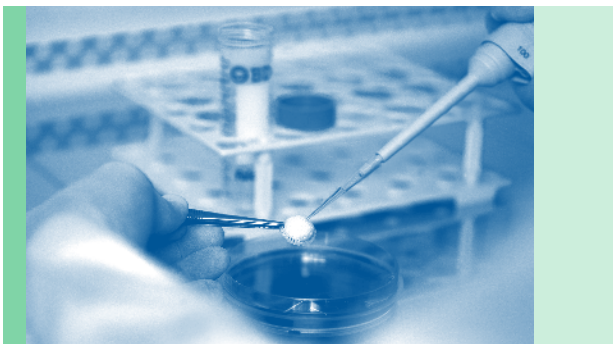
CBER regulates cellular and gene therapy products, including therapeutic cancer vaccines. Somatic cells, vectors expressing certain gene products, and genetically manipulated cells promise to harness the power of various cell types to fight disease, restore normal function, repair injuries, replace lost cells, or regenerate failing organs.

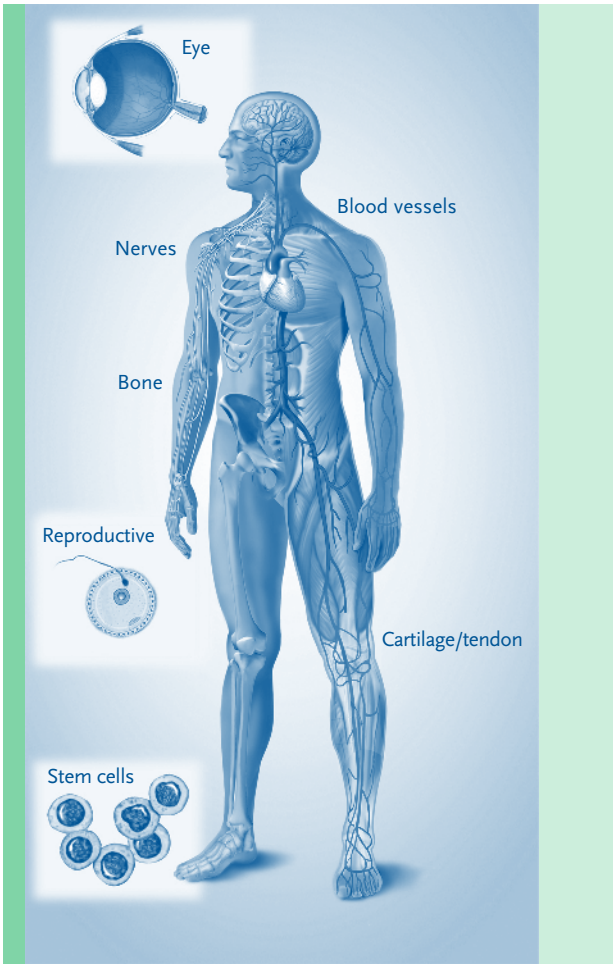
CBER is aware of both the promise of gene therapy and its potential to cause serious adverse events, and thus works closely with the National Institutes of Health (NIH), academia, and industry on these products. For example, FDA and NIH have collaboratively developed a web-accessible database on human gene transfer called the Genetic Modification Clinical Research Information System (GeMCRIS). GeMCRIS enables faster reporting of adverse events in human gene transfer trials, provides information to the public directly via the Internet at http://www.gemcris.od.nih.gov and improves the government's ability to monitor adverse events in gene therapy trials.

Manufacturers of gene and cellular therapy products must study their products in the laboratory for safety before beginning studies in humans under an Investigational New Drug (IND) application or an Investigational Device Exemption (IDE). As with all biological products, gene and cellular therapies are required to meet statutory and regulatory requirements for safety, purity, and potency before the products can be licensed for commercial distribution in the U.S.

CBER has provided proactive scientific and regulatory advice to manufacturers in areas of novel product development. Focusing on how best to evaluate essential issues of safety and efficacy, while facilitating product development, we are also committed to protecting human study subjects. Our involvement in broad public interactions helps CBER and product developers address important issues involving the development of novel gene and cellular therapy products.

As part of our mission-oriented research, CBER is studying the causes and mechanisms that may underlie certain gene therapy adverse events. Those particularly targeted include adenoviral and retroviral vectors; two of the most commonly used gene therapy vectors.





Tissues

Tissue transplantation is a rapidly growing industry. The number of musculoskeletal tissue transplants increased from approximately 350,000 in 1990, to more than 1.6 million in 2006. CBER is responsible for regulating many different types of human tissue and cells that are transplanted during various types of medical procedures (e.g., skin replacement following severe burns, tendons and ligaments used to repair injuries, bone replacement, and corneas used to restore eyesight).

Transplantation of human tissues presents unique safety challenges, in particular the risks of transmitting infectious diseases from donor to recipient and the contamination of tissues during processing. While these risks can be reduced significantly, they cannot be completely eliminated. Since 1993, CBER has required tissue establishments to screen and test donors; and since 1997, the Center has required tissue establishments to prepare, validate, and follow written procedures to prevent contamination and cross-contamination.

In response to the increasing uses and complexity of tissue transplants and the recognition of threats to tissue safety, CBER developed and implemented a comprehensive new framework for the regulation of human cells, tissues, and cellular- and tissue-based products. The new framework which went into effect in May 2005, promotes the use of the most up-to-date tools and methods to reduce risks of infectious disease transmission and contamination.

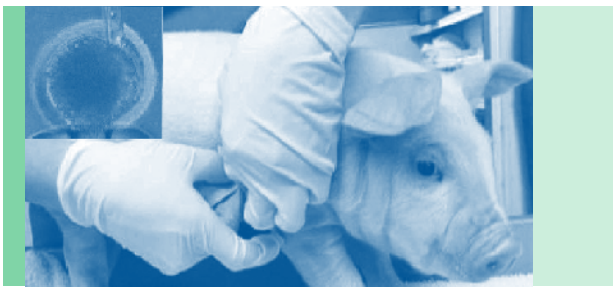
These new regulations encourage a comprehensive, yet flexible, approach to the entire manufacturing process, from donor eligibility to the distribution of final products and post-marketing adverse event reporting. CBER conducted extensive outreach and sought stakeholder input as we developed the regulatory framework, and we continue to seek input into this important area.

Xenotransplantation[22-24]

CBER regulates products used in xenotransplantation; which is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (a) live cells, tissues, or organs from a nonhuman animal source; or (b) human body fluids, cells, tissues, or organs that have had contact with live, nonhuman animal cells, tissues, or organs. CBER is also an international leader in efforts to ensure the safety and appropriate regulation of xenotransplantation products.

Xenotransplantation promises to provide needed organs and tissues to thousands of individuals who await transplants of scarce human organs. These new products also hold the potential for the treatment of a wide range of conditions and disorders, including diabetes, degenerative neurological disorders, and other diseases involving tissue destruction and organ failure.

Currently, the demand for human organs for clinical transplantation far exceeds the supply. However, although the potential benefits of xenotransplantation are considerable, it also poses complex scientific and public health challenges, most notably the risk of transmission of infectious diseases from animals to humans, and transplant rejection. CBER's continued careful oversight is critical to ensuring the public is protected during the developing and testing of these investigational therapies. Moreover, CBER also performs novel laboratory research into the mechanisms of immune rejection of xenotransplantation products and the potential infectious disease risks that these products may present.



Devices

CBER regulates many medical devices used in the collection, processing, testing, manufacturing, and administration of blood, blood components, human

cells, tissues, and cellular and tissue-based products. The Center's activities include regulation of HIV-1 and other infectious disease test kits used to screen donors of blood, blood components, and cells- and tissues. CBER also regulates HIV-1 tests used to diagnose, treat, and monitor therapy in persons infected with HIV.

CBER collaborates closely with FDA's CDRH on cross-cutting issues. We also work with CDRH and FDA's Office of Combination Products (OCP) to regulate combination products, such as tissue-engineering (TE) products.

The Center has also leveraged its resources by working with the National Toxicology Program (NTP), a joint FDA–NIH venture, to evaluate the safety of materials used in blood collection and transfusion devices.

Allergenics[25-28]

CBER licenses and regulates allergenic products, which include allergen patch tests and allergenic extracts.

Allergen patch tests are diagnostic tests applied to the surface of the skin to determine the specific causes of contact dermatitis, and are manufactured from natural substances or chemicals (nickel, rubber, and fragrance mixes) that are known to cause contact dermatitis.

Allergenic extracts are used to diagnose and treat allergic diseases, such as allergic rhinitis (or hay fever), allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy. CBER proactively evaluates novel technological approaches to improve allergenic product development and standardization, and characterizes these complex biological products.

Some allergenic extracts are currently standardized, while others are not. For standardized allergenic extracts, the potency is standardized by comparing them with U.S. reference standards, which CBER maintains and distributes to manufacturers.

PUBLIC HEALTH PREPAREDNESS

Pandemic Influenza Preparedness[29-30]

Pandemic influenza is a significant public health threat to our nation and the world.

Many nations are now developing plans to prepare for, and respond to, the next influenza pandemic. Scientists are concerned that the highly pathogenic avian influenza virus of the H5N1 subtype that currently circulates in wild and domestic birds in Asia, Europe, the Middle East, and Africa, might evolve into a form capable of efficient and sustained human-to-human transmission, triggering a global outbreak (or pandemic).

Preparedness planning is imperative to lessen the impact if such a pandemic should occur; and CBER plays a leadership role both domestically and internationally in preparations for and responses to the risks of a pandemic influenza outbreak.

Throughout FY 2007, CBER continued to facilitate the development of new influenza vaccines for seasonal and pandemic use by working with influenza vaccine manufacturers on scientific approaches, issuing guidances for influenza vaccine development, and furthering research that supports pandemic-related activities.

International Activities

As part of its mission to protect the health of people in the U.S. and worldwide, CBER is working to license pandemic influenza vaccines for use in the U.S., and globally.

In order to achieve this goal, CBER works with the World Health Organization (WHO), foreign national regulatory authorities, and manufacturers to encourage cooperative research, more efficient product development, and the development of common scientific standards for safety, potency, and effectiveness.

For example, CBER has been a co-leader with WHO and Health Canada in three technical workshops on pandemic influenza vaccine development and production. These workshops included representatives from the national regulatory authorities of influenza vaccine-producing countries and countries interested in exploring influenza vaccine production. The most recent workshop (Geneva, June 2007) was convened to continue development of the WHO Guidelines on Regulatory Preparedness for Human Pandemic Influenza Vaccines, which is expected to be adopted and released by WHO. CBER experts also participated in other WHO consultations on pandemic influenza issues, including the establishment of a WHO strategic stockpile of H5N1 influenza vaccines.

In previous years, CBER established a collaborative relationship with the European Medicines Agency (EMEA) to expedite exchange of information on pandemic influenza products in the regulatory pipeline. In FY 2007, fruitful interactions and exchanges continued and included discussions between scientists of the respective agencies to collaborate on developing harmonized procedures, where possible, and to evaluate submissions in each agency's influenza vaccine portfolio.

In May 2007, CBER worked with colleagues at FDA to convene a "Pandemic Influenza GMP Workshop" for an audience of foreign regulatory counterparts. The workshop brought together regulators from 16 different nations to discuss development of medical countermeasures for influenza and related current Good Manufacturing Practices (cGMP) issues.

CBER Director, Jesse L. Goodman, M.D., M.P.H., and FDA Commissioner, Andrew von Eschenbach, M.D., participated in the 2007 Pacific Health Summit sponsored by the National Bureau of Asian Research, the Bill & Melinda Gates Foundation, and the Fred Hutchinson Cancer Research Center. The theme for the summit was "Pandemics: Working Together for an Effective and Equitable Response." Dr. von Eschenbach gave one of five keynote addresses. Dr. Goodman participated in panel discussions and strategic discussions on pandemic preparedness with a focus group that included the Director-General of WHO, Dr. Margaret Chan. The summit brought together experts on existing global scientific collaborations, and sought to strengthen prevention and preparedness, especially among those populations most vulnerable to pandemic influenza and other emerging infectious diseases.

First U.S. Vaccine for Humans Against the Avian Influenza Virus H5N1

On April 17, 2007, CBER approved the first U.S. vaccine for humans against the H5N1 influenza virus. The vaccine is designed for use if the current H5N1 virus acquires the ability to efficiently spread from human to human potentially triggering an outbreak that rapidly spreads around the world. People will have little immunity to this virus. Should such an influenza pandemic emerge, the vaccine might provide early limited protection in the months before a vaccine tailored to the pandemic strain of the virus could be developed and produced.

So far, H5N1 influenza has remained primarily an animal disease, and the human cases were most likely the result of animal-to-human transmission, with human exposure to sick or dead birds probably being the primary risk factor.

"The threat of an influenza pandemic is, at present, one of the most significant public health issues our nation and world faces," said Andrew C. von Eschenbach, M.D. "The approval of this vaccine is an important step forward in our protection against a pandemic."

The H5N1 virus is one version of the influenza A virus commonly found in migratory, aquatic birds. In comparison with seasonal influenza, the human disease caused by H5N1 is far more severe, commonly causing pneumonia, multi-organ failure, and death in the majority of individuals.

Although there have been no reported human cases of H5N1 infection in the U.S., WHO has confirmed that more than 300 people worldwide have been infected with this virus since 2003, and more than 200 of them have died.

"The timing and severity of an influenza pandemic are uncertain, but the danger remains very real," said Jesse L. Goodman, M.D., M.P.H. "We are working closely with other government agencies, global partners, and the vaccine industry to facilitate the development, licensure, and availability of needed supplies of safe and effective vaccines to protect against the pandemic threat."

In cooperation with FDA, NIH, and other government agencies, manufacturers are developing a next generation of influenza vaccines designed to confer enhanced immunity to H5N1 using a smaller amount of viral antigen per dose.

The approval and availability of this H5N1 vaccine will enhance national readiness and the nation's ability to protect those at increased risk of exposure.

A Sixth Seasonal Influenza Vaccine

On September 28, 2007, CBER approved Afluria, an inactivated seasonal influenza vaccine for the immunization of people ages 18 and older. Afluria is intended to protect adults from influenza type A and type B viruses. The approval of Afluria is noteworthy because it represents the sixth influenza vaccine manufacturer licensed to bring these products to market. This vaccine enhances our ability to produce influenza vaccine and thus significantly contributes to the nation's pandemic preparedness. Based on current manufacturing trends, the CDC estimated the six manufacturers would supply a record 134 million doses of influenza vaccine for the 2007–2008 influenza season.

Afluria was approved using FDA's accelerated approval pathway for serious or life-threatening diseases, which reduces the time it takes to make important medical products available to the public. As part of the accelerated approval process, the manufacturer will conduct further studies to verify the vaccine decreases seasonal influenza disease after vaccination.

"Routine immunization is the most effective way to prevent influenza and decrease influenza-related complications, which can include serious illness and death," said Jesse L. Goodman, M.D., M.P.H. "The licensure of this additional manufacturer contributes to having an adequate supply of seasonal influenza vaccine for Americans, one of FDA's highest priorities."

Flu season in the U.S. can begin as early as October and can last as late as May, according to the CDC. Every year in the U.S., more than 200,000 people are hospitalized with influenza, and approximately 36,000 people die from its complications. Although it is best to be immunized as soon as the vaccine is available, usually in September, getting a flu shot any time during influenza season is also appropriate because the influenza season often peaks late.

Expansion of Indication for Nasal Influenza Vaccine

In September 2007, CBER also approved the expansion of the population that could use the nasal influenza vaccine, FluMist, to include children between the ages of 2 and 5. This vaccine contains a weakened form of the live virus predicted to circulate in the population for any given season and is sprayed in the nose. This approval was significant because, until then, approved use of the vaccine was limited to healthy children age 5 and older and to adults up to age 49. Moreover, there were only two vaccines licensed in the U.S. for children under the age of 5: (1) Fluzone, for use in children over age 6 months, and (2) Fluvirin, for use in children age 4 and older.

"The goal of preventing influenza is now more attainable with the availability of FluMist for younger children," said Jesse L. Goodman, M.D., M.P.H. "This approval also offers parents and health professionals a needle-free option for toddlers, who may be reluctant to get a traditional influenza shot."

The CDC recommends that all children age 6 months to 59 months receive a vaccination to protect against influenza. Studies have shown that children younger than age 5 had rates of influenza-associated hospitalizations similar to those among individuals age 50 through 64, which highlighted the need for improved influenza prevention efforts for this younger U.S. population.

Two Final Influenza-Related Guidance Documents

The FDA is working to increase the supply of safe and effective influenza vaccines by outlining regulatory pathways that will expedite the development and approval of these products.

As part of that effort, CBER finalized and released in May 2007 the following two guidance documents that will assist manufacturers in developing and evaluating new vaccines for seasonal and pandemic influenza:

- Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.

These guidances reflect both the goals of FDA's Critical Path Initiative and the role of CBER as a science-based regulatory organization that helps industry translate scientific advances into new medical products while shortening the approval process.

H5N1 Clade 2 Reference Strain for Pandemic Vaccine Production

New variants of H5N1 viruses continue to emerge and it is important to make new reference strains from these variants that can be used in vaccine manufacturing. CBER used reverse genetics techniques to generate the A/duck/Laos/3295/2006 reassortant strain of H5N1. This reassortant contains the internal genes of A/Puerto Rico/8/34, which is the backbone of the viruses that grow rapidly in cultures and are used to represent candidates for full development into vaccines. This reassortant strain also contains the genetically modified hemagglutinin (HA) and wild-type neuraminidase (NA) of A/duck/Laos/3295/2006, subtype H5N1, clade 2.3.

The genetic modification of the HA removed the polybasic amino acid cleavage site, which confers the natural virus's high pathogenicity. While this new reassortant is therefore expected to be nonpathogenic, that hypothesis is currently being tested through in vitro and in vivo testing at St. Jude Children's Research Hospital. Should this reassortant's nonpathogenicity be confirmed, application will be made to the U.S. Department of Agriculture (USDA) and CDC for a select agent exclusion request. Following approval of such a request, FDA would make this reassortant available as a vaccine candidate for production of CLADE 2.3 pandemic

influenza vaccines.

CBER is also participating in the Interagency Influenza Diagnostic Working Group, the CDRH Pandemic Flu Task Force, and the Project Coordination Team of the Biomedical Advance Research and Development Authority (BARDA) to facilitate the development of assays for pandemic influenza - particularly the highly pathogenic avian influenza strain H5N1. This coordinated effort is designed to help generate reference panels and reagents for validation and approval of influenza diagnostics that can be rapidly adapted for other indications, including blood donor testing, if necessary. CBER is also conducting research on assays for detection of major pandemic influenza strains.

Other Ongoing Pandemic Influenza Preparedness Efforts

CBER is currently enhancing pandemic preparedness in the following ways:

- Participating with WHO as a reference reagent laboratory for seasonal influenza (http://www.who.int/csr/disease/influenza/collabcentres/en/); collaborating closely with global regulatory entities and industry partners to generate and make available both seasonal and pandemic influenza vaccine potency reagents.
- Collaborating with global regulatory entities, industry, academia and others, to develop and validate new assays to measure the human immune response to pandemic influenza vaccines and to measure vaccine potency.
- Soliciting input from scientific experts on prime/boost strategies for new candidate pandemic influenza vaccines. For example CBER organized and convened the Vaccines and Related Biological Products Advisory Committee (VRBPAC), and devoted a special session to this topic.
- Developing new molecular tools to help evaluate pandemic influenza vaccines and initiating collaborative research projects, including developing assays and genetic safety markers for influenza vaccines.
- Designing pathways for emergency responses to sustain local supplies of critical blood products if available blood donors and blood center staff decrease because of a pandemic outbreak.
- Participating in various Department of Health and Human Services (DHHS) pandemic influenza efforts, including working groups and subgroups related to vaccine production and other pandemic influenza medical countermeasures.
- Maintaining and developing staff to review IND applications for influenza vaccine candidates under development.

Emergency Response Planning

CBER has developed and maintains a comprehensive and effective program to ensure the continuity of essential government functions under all circumstances. CBER has identified essential functions; developed methods to safeguard personnel, records, and facilities; planned for acquisition of emergency resources; and ensured its capability to perform at alternate work sites until normal operations can be resumed.

CBER has integrated, as part of its Continuity of Operations (COOP) preparedness, an Emergency/Event Notification (EEN) System. This system enables CBER to rapidly and automatically contact all COOP personnel through simultaneous notification of an individual's electronic mail account, as well as home, work, and cellular telephone numbers. The EEN System will leave a voice message if a telephone call is not answered.

CBER conducts quarterly testing of COOP alert, notification, communication, and activation/relocation procedures. CBER also conducts an annual review of all COOP plans.

Information Technology Emergency/Pandemic Response Plan

To support CBER's Pandemic Influenza Program, CBER is coordinating several projects with FDA, the Office of the Chief Information Officer (OCIO), and the Office of Information Technology Shared Services (OITSS). These projects will ensure remote access during a crisis, database replication, and disaster recovery. Both the Citrix Remote Access for Pandemic Influenza staff and the High-Availability Database Replication projects have procured the necessary software and hardware; and the design of network architecture design, installation of equipment, and implementation of the system steadily progressed in FY 2007. CBER offices continue to pilot the Web

Collaboration Project, which provides an online meeting tool for use with internal and external organizations.

Protecting America from Terrorism

CBER is responsible for helping to ensure that safe and effective biological products are available to treat and prevent illness due to potential terrorist agents. CBER interacts intensively with DHHS, Department of Homeland Security (DHS), Department of Defense (DoD), and industry on many projects aimed at making our nation better prepared for biological, chemical, and radiological/nuclear terrorism.

CBER has provided extensive support to the BARDA, within the office of the Assistant Secretary for Preparedness and Response (ASPR), DHHS; and has reviewed and provided technical input on multiple requests for proposals (RFPs) for acquisition of additional countermeasures for the Strategic National Stockpile (SNS) such as anthrax therapeutics, new smallpox vaccines, botulinum antitoxin, new anthrax vaccines, and neutropenia. CBER also provided guidance on the types of data the Center would require if asked to consider use of unapproved countermeasures under an Emergency Use Authorization (EUA) such as modified vaccinia ankara smallpox vaccine, anthrax immunoglobulin, botulinum antitoxin, and rPA anthrax vaccine. CBER participated in DHHS-led meetings under the new structure relevant to biological products, such as Project Coordination Team meetings, Integrated Program Team meetings, and Enterprise Executive Committee meetings.

CBER led the effort to develop and finalize new labeling regulations for medical products purchased for the SNS. The Interim Final Rule was published in the Federal Register on December 28, 2007. This rule permits FDA Center Directors to grant exceptions or alternatives to certain regulatory labeling requirements applicable to human drugs, biological products, or medical devices that are or will be held in the SNS. The goal of this rule is to ensure the safety, effectiveness, and availability of appropriate medical countermeasures in the event of a public health emergency. Under this rule, an exception or alternative to certain labeling requirements may be granted if it is determined that compliance with the existing labeling requirements could adversely affect the safety, effectiveness, or availability of specified lots, batches, or other units of human drugs, biological products, or medical devices that are or will be included in the SNS. The rule does not allow for exceptions or alternatives to labeling that are explicitly required by statute.

Second-Generation Smallpox Vaccine with Medication Guide and Risk Minimization Action Plan[31]

On August 31, 2007, CBER licensed a new vaccine to protect against smallpox, a highly contagious disease with the potential to be used as a bioterror weapon. The vaccine, ACAM2000, is intended to protect people at high risk of exposure to smallpox and could be used to protect individuals and populations during a bioterrorist attack. The licensure of ACAM2000 enhances U.S. preparedness for an emergency, such as a bioterrorist attack in which the smallpox virus is used as a weapon. This vaccine will be part of the SNS of medical supplies maintained by CDC.

"The licensure of ACAM2000 supplements our current supply of smallpox vaccine, meaning we are more prepared to protect the population should the virus ever be used as a weapon," said Jesse L. Goodman, M.D., M.P.H. "This vaccine is manufactured using modern cell culture technology allowing rapid and large-scale production of a vaccine with consistent product quality." The only other FDA licensed smallpox vaccine, Dryvax, was approved more than 50 years ago, is no longer manufactured, and is in short supply.

A worldwide vaccination program eradicated smallpox in the population. The last case of naturally occurring smallpox in the U.S. was in 1949, and the last case in the world was reported in Somalia in 1977. Smallpox virus is known to be kept only in two approved laboratories in the United States and Russia. The CDC considers it a Category A agent, meaning it presents one of the greatest potential threats for harming public health. There is no FDA-approved treatment for smallpox, and the only prevention is vaccination.

"Smallpox could be a particularly dangerous biological threat to us that would kill or debilitate a high percentage of the population," said Rear Admiral W. Craig Vanderwagen, M.D., Assistant Secretary for Preparedness and Response, DHHS. "The licensing of ACAM2000 will make us better prepared as a nation because it provides an important, effective tool for protecting first responders and individuals with a high risk of exposure from this potentially lethal disease."

ACAM2000 contains live vaccinia virus, which means special care must be taken to prevent the virus spreading from the inoculation site to other parts of the body and to other individuals. To minimize known risks, and to ensure the vaccine is given safely and effectively, the vaccine licensing is subject to a Risk Minimization Action Plan (RiskMAP). The RiskMAP

requires providers of the vaccine and patients to be educated about these risks and requires patient education through an FDA-approved Medication Guide for those who receive the vaccine.

The Medication Guide explains the proper care of the vaccination site and provides information about serious side effects that can occur with ACAM2000. Studies have shown that approximately 1 in 175 healthy adults who received smallpox vaccine for the first time developed inflammation and swelling of the heart and/or surrounding tissues (myocarditis and/or pericarditis).

Partnership with the National Institute of Allergy and Infectious Diseases to Facilitate New Vaccine Development Against Bioterrorism Agents[12, 18, 32]

Despite many important discoveries in research designed to address medical countermeasures to bioterrorism agents and rapidly emerging infectious diseases (REIDs), few of these discoveries have been translated into vaccines, drugs, and diagnostics that benefit the public health. Therefore, there is a critical need for practical and reproducible tests and model systems that demonstrate these new innovations (such as vaccines) are pure, safe, immunogenic, and effective.

A partnership established in July 2006 combines the skills of the NIH/National Institute of Allergy and Infectious Diseases (NIAID) in managing infectious disease research and development, with CBER's mission to facilitate the development of safe and effective products through research and regulation of products.

The major goals of the partnership are to:

- facilitate the rapid development of novel vaccine products, especially for bioterrorism agents and REID that are supported by NIAID/NIH and meet the regulatory requirements of FDA
- develop practical and reproducible tests and model systems that help evaluate whether these new innovations are safe, immunogenic, and effective
- accelerate the pathway of potential candidates into human clinical trials, licensure, and use by the public.

In the first year of this partnership (2007), accomplishments include:

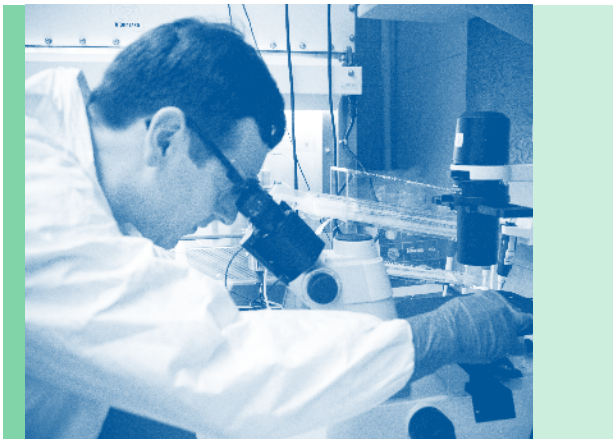
- development of a standardized assay to evaluate new plague vaccines and reference reagents to be delivered to NIAID-supported plague vaccine developers
- production of high-quality botulinum toxoids that are 100,000 times more immunogenic than the toxoids currently being supplied to NIAID researchers by current suppliers
- standardization of a potency assay for smallpox vaccines.

Postmarketing Efforts

CDC/Harvard Influenza Vaccine Safety Surveillance Healthcare Database Project

CBER is collaborating with the CDC, Harvard University, Harvard Pilgrim Health Care, and United Health Care to explore, plan, and expand the ability of the Vaccine Safety Datalink to perform rapid cycle analysis that includes the United Health Group. The expansion of the Vaccine Safety Datalink, which is a database that studies vaccine safety issues, would be critical during an influenza pandemic or other urgent vaccine safety incident, and would enable tracking of selected adverse events related to widely administered pandemic vaccines. CBER is also collaborating with Centers for Medicare & Medicaid Services databases in this advanced use of information technology to monitor influenza vaccine safety.

INNOVATIVE PRODUCTS AND NOVEL TECHNOLOGIES



Robert W Fisher, Ph.D., Laboratory of Plasma Derivatives, Office of Blood Research and Review, CBER

First Biological Product for Treatment of Patients with von Willebrand Disease Undergoing Surgical and Invasive Procedures

On February 2, 2007, CBER approved Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate, manufactured by Grifols Biologicals, Inc., for use in patients with von Willebrand disease (vWD) undergoing surgery or invasive procedures in whom the hormone desmopressin is either ineffective or contraindicated. It is not approved for patients with severe vWD (Type 3) who are undergoing major surgery. Von Willebrand disease is the most commonly inherited bleeding disorder, affecting about 1% of the U.S. population.

Alphanate is the first biological product approved for treatment of patients with vWD undergoing surgical and invasive procedures. Alphanate is already approved for the prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A or acquired Factor VIII deficiency.

"This approval is an important advance for patients and their surgeons, providing them access to a proven preventive therapy that can make needed surgery possible and safer," said Jesse L. Goodman, M.D., M.P.H.

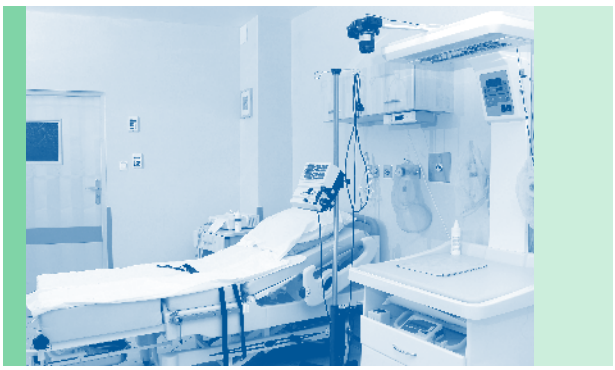
Expanded Use for Antihemophilic Factor/von Willebrand Factor Complex

On April 27, 2007, CBER approved Humate-P (Antihemophilic Factor/von Willebrand Factor Complex), manufactured by CSL Behring, for the prevention of excessive bleeding during and after surgery in certain patients with mild-to-moderate and severe vWD. This product was originally approved for use in adult patients to treat and prevent bleeding from hemophilia A and was later approved to treat spontaneous and traumatic bleeding for severe vWD and mild and moderate vWD when desmopressin use is known or suspected to be inadequate.

Humate-P is the second biological product to be approved for the management of surgery and invasive procedures in patients with vWD in whom the medication desmopressin may not work. Humate-P is the first product developed specifically for patients with severe vWD who are undergoing major surgery.

"This is an important advance for patients with vWD, including those who are severely affected by the disorder," said Jesse L. Goodman, M.D., M.P.H. "Humate-P provides a preventive therapy that can make needed surgery not only possible, but also safer."

Humate-P is made by purifying the clotting protein from human plasma obtained from carefully screened and tested U.S. donors and undergoes processing to further reduce the risk for transfusion-transmitted diseases.



First Biological Product to Treat Rare Clotting Disorder

On March 30, 2007, CBER licensed Ceprotin, the first biological treatment for patients with severe congenital Protein C deficiency, a rare genetic defect that can cause a potentially life-threatening clotting disorder. Ceprotin, manufactured by Baxter Healthcare Corporation, is made from the plasma of healthy human blood donors. It is a concentrated form of Protein C, a substance normally manufactured in the liver and released to circulate in the plasma. Protein C plays an important role in controlling blood coagulation by preventing the formation and growth of blood clots.

Severe congenital Protein C deficiency occurs in one to two of every million newborns. Patients with insufficient levels of Protein C suffer abnormally high numbers of blood clots; and complete absence of the protein is fatal. Patients with severe inherited Protein C deficiency must take oral or injected anticoagulant drugs on a regular, lifelong basis to avoid blood clots. Ceprotin is intended to treat these patients when they are faced with a life-threatening situation from blood clots in the veins, or a severe skin and systemic blood clotting disorder known as Purpura fulminans.

CBER reviewed the product's Biologics License Application (BLA) under a priority review schedule. CBER granted Ceprotin orphan drug status. Orphan drug status provides the manufacturer with financial incentives to develop a drug or biologic to treat a rare disease affecting fewer than 200,000 people in the U.S. Since 1983, more than 200 drugs and biological products have been brought to market in this way.

Human Thrombin for Topical Use in Surgery

On August 27, 2007, CBER approved Evithrom, manufactured by OMRIX Biopharmaceuticals, Ltd., a blood-clotting protein used to help control bleeding during surgery. It is derived from human plasma obtained from carefully screened and tested U.S. donors and has undergone processing to further reduce the risk for transfusion-transmitted diseases.

Evithrom is indicated as an aid to stop oozing and minor bleeding from capillaries and small veins, and when control of bleeding by standard surgical techniques is ineffective or impractical.

"The approval of Evithrom offers an important additional option for surgeons and their patients to help control surgical bleeding," said Jesse L. Goodman, M.D., M.P.H.

Novel Assay for the Diagnosis of HIV Infections[33]

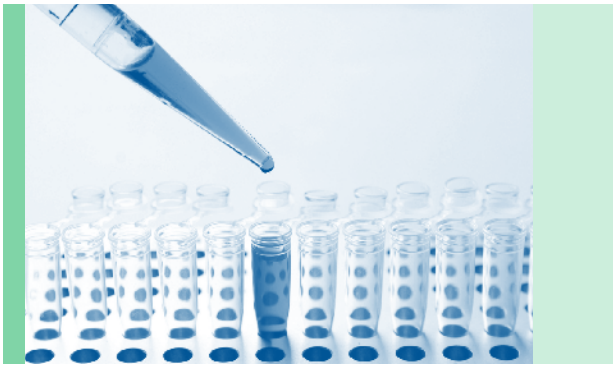
All current HIV vaccine candidates contain multiple viral components and elicit antibodies that react positively in licensed HIV diagnostic tests that contain similar viral products. HIV vaccine recipients might have a positive screening test for HIV infection even though they are not infected. Further testing of these individuals would confirm that they not infected. Nevertheless, given that many HIV vaccines are under development on a global basis, it is important to have a test that rapidly differentiates between HIV infection-induced antibodies and vaccination-induced antibodies.

In response to this issue, CBER developed a new test to differentiate HIV-infected individuals from those whose antibodies reflect immune response to vaccination.

Using the whole HIV genome phage display library, CBER scientists identified conserved sequences in two HIV proteins (Env-gp41 and Gag-p6) that are recognized soon after infection, do not contain protective epitopes, and are not part of the most current HIV vaccines. Based on these proteins, CBER laboratories developed a new HIV serodetection assay called HIV-SELECTEST that has greater than 99 percent specificity and sensitivity.

Importantly, HIV-Selectest screening of plasma samples from multiple HIV vaccine trials differentiated and identified uninfected trial participants, who had a negative test result, while all intercurrent infections were detected within 1–3 months of HIV infection.

Collaborative studies completed in 2007, demonstrated the HIV-SELECTEST is equally sensitive in detecting early HIV infections in men and women regardless of the clades. A rapid test version of the HIV-SELECTEST is now under development for easier point-of-care



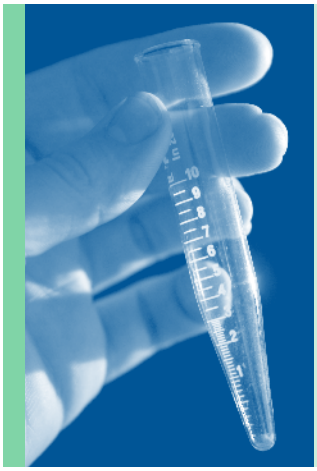
testing during vaccine trials. Ultimately, the new HIV-SELECTEST will provide a simple, but robust, diagnostic tool for easy implementation in HIV vaccine trials and blood banks.

New Assays for Monitoring HIV-1 Viral Load in Drug-Treated Patients

On May 11, 2007, CBER approved two viral load assays, Abbott RealTime HIV-1 assay and COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Molecular Systems). The Abbott RealTime HIV-1 assay, for use on the new m2000 system, is designed to detect and precisely measure levels of the HIV circulating in a patient's blood (viral load), including the three major groups of HIV-1 and non-B subtypes. The test is intended for use as a marker of disease prognosis and as an aid in assessing viral response to antiretroviral treatment.

This ability of this new test to measure non-B subtypes of HIV is important because although subtype B continues to be the most common strain found in the U.S., studies suggest an increasing number of newly diagnosed patients are infected with non-B subtype viruses. A recent study by the CDC, involving more than 3,000 HIV patients in the U.S. found that 5.1 percent of those patients were infected with HIV-1 non-B subtypes.

The Abbott RealTime HIV-1 test was developed for use on the Abbott m2000 system, an automated instrument for DNA and RNA testing in molecular laboratories. The m2000 system is based on real-time polymerase chain reaction (PCR) technology and is designed to efficiently detect and measure life-threatening viruses and bacteria in patient samples in less than 5 hours, compared with other testing methods that may take up to 2 days.



The Cobas AmpliPrep/Cobas TaqMan HIV-1 Test is a fully automated HIV-1 diagnostic tool that uses real-time PCR technology.

This assay provides a broader range of viral load data than earlier generation tests, quantifying the amount of virus in the blood from very high to very low levels. Laboratories can now deliver highly accurate results faster—a decisive advantage for doctors monitoring how well a chosen therapy is working for the patient.

Prevention of Hepatitis B Reinfection in Liver Transplant Patients

On April 6, 2007, CBER approved HepaGam B, manufactured by Cangene Corportation, for the prevention of hepatitis B reinfection in certain liver transplant patients. HepaGam B, an immune globulin product, is the first product of its kind approved for this purpose.

Hepatitis B is a serious disease caused by a virus that attacks the liver, possibly causing lifelong infection, liver cancer, liver failure, or even death. Liver transplant patients who have already been exposed to HBV are at an increased risk of reinfection because of their weakened immune systems.

HepaGam B provides an immediate immune response to the virus, thus protecting patients previously exposed to HBV. Patients must receive injections at the time of their liver transplant and throughout their lives. This product is manufactured from human plasma collected from healthy donors at U.S.-licensed plasma centers.

Fully Automated System for Qualitative Detection of Antibodies to HCV

On July 12, 2007, CBER approved the Abbott PRISM HCV Assay, an in vitro chemiluminescent immunoassay (ChLIA) that uses a novel technology for the qualitative detection of antibodies to HCV (anti-HCV).

The Abbott PRISM HCV Assay is intended to screen for the presence of anti-HCV in individual donors, including volunteer donors of whole blood and blood components, and other living donors. It is also intended for use in testing blood and plasma specimens to screen organ donors when specimens are obtained while the donor's heart is still beating; and for testing blood specimens to screen cadaveric (non-heart-beating) donors. It is not intended for use on cord blood specimens or for the diagnosis of HCV infection.

Abbott PRISM HCV Assay is highly sensitive and specific for the detection of anti-HCV. It is fully automated, reducing the potential for operator errors and is also tamper-resistant, with redundant checks to ensure integrity of the system.

Procleix Ultrio Assay on the Fully Automated Procleix TIGRIS System

On May 23, 2007, CBER approved the BLA Supplement for the Procleix Ultrio Assay that permitted the use of the Procleix TIGRIS System with the Assay.

This is the first fully automated, qualitative in vitro NAT to screen for HIV-1 and HCV ribonucleic acid in individual donations or pools of human plasma when pools are comprised of equal aliquots, or samples representative of the whole, of not more than 16 individual donations from donors of whole blood, blood components, or source plasma. It is also intended for use in testing plasma and serum specimens to screen organ donors when specimens are obtained while the donor's heart is still beating; and in testing blood specimens from cadaveric donors. The capability of full automation will enhance compliance with cGMP by reducing human error while accelerating blood screening and enhancing blood safety.

Draft Guidance Streamlining the Licensure Path for Certain Placental/Umbilical Cord Blood Products Intended for Hematopoietic Reconstitution

On January 16, 2007, FDA issued a draft guidance entitled: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies which recommended a streamlined path to licensure for manufacturers of cord blood for certain medical conditions. Placental/umbilical cord blood is a rich source of precursor cells capable of differentiating into mature blood cells. These precursor cells are known as hematopoietic stem/progenitor cells, and they can be used to replenish the bone marrow in patients with blood-based malignancies, such as leukemia.

"Cord blood hematopoietic stem/progenitor cells offer the potential for tremendous therapeutic benefit," said

Jesse L. Goodman, M.D., M.P.H. "In this draft guidance, FDA provides recommendations on a streamlined path to licensure for these promising products that also ensures their safety and effectiveness."

The draft guidance describes FDA's approach to the regulation of cord blood hematopoietic stem/progenitor cells that are:

- minimally manipulated (processing does not alter the original characteristics of the cells)
- used to replenish the bone marrow in patients with blood-related malignancies
- used in recipients unrelated to the donor of the stem cells.

For a copy of the guidance, visit: http://www.fda.gov/cber/gdlns/cordbld.pdf.

Critical Path[34-59]

In 2004, FDA began focusing on the critical path that medical products must travel, from the earliest stages of development to their use in patients. The Critical Path Initiative is FDA's strategy for stimulating and facilitating a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured. The Critical Path Initiative also will enable FDA to make regulatory decisions that will shape personalized medicine in this new age of molecular medicine.

FDA initiated this strategy by working with the academic community, the public, the pharmaceutical industry, and other federal health agencies to identify projects most likely to modernize and transform the development and use of medicines. Following consultation with stakeholders in 2006, FDA published the Critical Path Opportunities Report and List. The report details 76 specific scientific projects that show great promise for smoothing the path from laboratory to bedside. The priority topics contained in the list include: better evaluation tools; streamlining clinical trials; harnessing bioinformatics; integrating the latest technology into product manufacturing; developing products to address urgent public health needs; and specific, at-risk populations, including pediatrics. In December 2006, FDA announced an additional 40 very promising scientific projects that are underway. The Opportunities List is available at the FDA website at http://www.fda.gov/oc/initiatives/criticalpath.

CBER has a long-standing record of improving regulatory pathways and facilitating the development and availability of safe, effective, and high-quality biological products. We accomplish this through research conducted by CBER scientists on vaccines, blood and blood products, cell, tissue, and gene therapies, and allergenics.

CBER is a key player in the Critical Path Initiative, and is engaged in the following Critical Path projects:

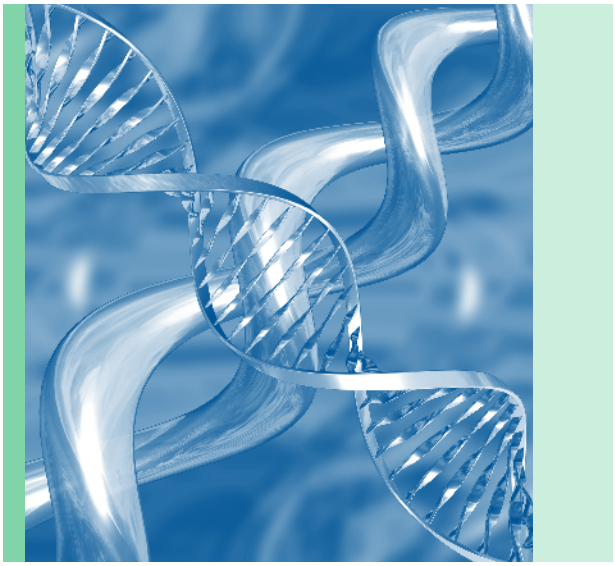
- cell substrates and novel adjuvants or assays to assess safety and quality
- investigations of the risk of insertional mutagenesis with retroviral vectored gene therapy
- animal models for vaccine efficacy for terrorism agents and other emerging threats
- influenza vaccine safety, quality, assays, and new technologies
- strategies to reduce carcinogenesis risks to enhance the safety of gene therapies
- collaboration with the National Institute of Environmental Health Sciences (NIEHS) as part of the National Toxicology Program to investigate the risk of insertional mutagenesis with retroviral vectored gene therapies
- improving predictive understanding of quality, distribution, effectiveness, and fate of genes and stem cells
- blood and tissue variant Creutzfeldt-Jakob Disease (vCJD) risk reduction, manufacturing safety, and assays
- emerging infectious diseases preparedness, including medical countermeasures (vaccines, immunoglobulins) and blood safety assays/ standards (e.g., Chagas, malaria)
- characterization/safety of "blood substitutes"
- advanced Bayesian/adaptive study designs and clinical study modeling
- enhanced use of and analytic tools for large databases and safety surveillance for influenza vaccines
- new tools for product characterization and quality (e.g., nuclear magnetic resonance and mass spectrometry); collaborative programs, including with CDC in influenza vaccine assays.

CBER established the Collaborative Scientific Training Program (CSTP) to facilitate research and training partnerships that engage scientific partners in pursuing goals of FDA's Critical Path Initiative. CSTP partnerships provide opportunities to join national and international scientific institutions, as well as opportunities for experts and trainees to synergize CBER's unique scientific and regulatory expertise with the complementary scientific knowledge and skills of collaborators.

Tissue Engineering

CBER is in a unique position to identify and address challenges to the development of innovative products, such as Tissue Engineering (TE).

CBER focuses simultaneously on the details of numerous specific product development plans through review of submitted applications for clinical trials, and thereby observe trends across an emerging, still fragmented, therapeutic field.



CBER provides guidance to manufacturers on product development that incorporates both scientific advances and FDA regulations; and participates in Multi-Agency Tissue Engineering Science group (MATES) tasked with priority setting, and nonconfidential information-sharing among agencies.

CBER participates in several international standards organizations, such as the American Society for Testing and Materials and the International Standards Organization as well as harmonization efforts with the International Conference on Harmonization and the Global Harmonization Task Force.

In addition, a CBER/CDRH Tissue Engineering Cross-Center Team was formed in FY 2007. CBER participants include representatives from the Office of Cellular, Tissue, and Gene Therapies and the Office of Compliance and Biologics Quality. This team facilitates intercenter cooperation and solutions to TE regulatory issues. This team also provides a core resource of TE review expertise to CBER, CDRH, and FDA's Office of Combination Products; participates in developing regulatory policy and pathways; facilitates FDA participation in standards organizations; provides a strong, consistent FDA voice in outreach activities with academia, industry, and other government programs.

BIOLOGICAL PRODUCT QUALITY AND AVAILABILITY

Melkamu Getie-Kebtie, Ph.D. and Peter Franke, Tumor, Vaccines and Biotechnology Branch Office of Cellular, Tissue and Gene Therapies, CBER

Human Tissue Program and Interdisciplinary Tissue Safety Team[59]

In an effort to evaluate and strengthen the Agency's risk-based system for regulating human cells, tissues, and cellular- and tissue-based products, FDA formed the Human Tissue Task Force (HTTF) in August 2006. The primary goal of the HTTF is to assess the challenges to implementing the risk-based tissue regulations in 2005 and identify additional steps that might be necessary to prevent the transmission of communicable disease while ensuring the availability of safe products. One of the issues addressed by the HTTF was the failure of two tissue recovery establishments to follow basic federal requirements for donor screening, testing, and tissue recovery.

The Task Force recommended targeted inspections of U.S. companies that recover human tissue. Under this initiative, the Office of Regulatory Affairs (ORA) inspected 153 high-priority tissue firms by the end of the second quarter of FY 2007. Although some deviations from the regulations were identified, no major inaccuracies or deficiencies were found. Based on the inspections, the Task Force concluded nearly all tissue recovery firms were in substantial compliance with the tissue regulations. The Task Force also made several recommendations on how to enhance tissue safety activities. CBER will use this information to develop and revise guidance documents, regulations, and future inspection strategies.

The Tissue Safety Team (TST), established in late FY 2004, increases safety by enhancing collaboration and coordination of stakeholder activities, evaluating products and responding to complex and emerging safety issues. TST also develops procedures and policies to evaluate adverse reactions and to facilitate rapid and comprehensive responses by the FDA and other agencies. The safety team is composed of experts from several disciplines, including product manufacturing, safety, clinical, compliance, epidemiology, and communications.

The TST enhances information-sharing and analytic processes for key product safety activities by taking an integrated multidisciplinary approach to early detection, analysis, action, and communication. The team meets on a regular basis and is ready for activation in the event of an emerging situation. The team also helps identify and implement long-term priorities, innovative practices and collaborations, and opportunities for quality improvement. The team collaborates with members of ORA, CDC, and other offices and agencies.

Significant accomplishments and guidances to promote tissue safety in FY 2007 include the issuance of three final rules and nine guidances for industry:

- Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular- and Tissue-Based Products—Small Entity Compliance Guide
- Draft Guidance for Industry: Eligibility for Donors of Human Cells, Tissues, and Cellular- and Tissue-Based Products
- Final Guidance to Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular- and Tissue-Based Products
- Final Guidance to Industry: Certain Human Cells, Tissues, and Cellular- and Tissue-Based Products Recovered from Donors Who Were Tested for

Communicable Diseases Using Pooled Specimens or Diagnostic tests

- Final Guidance for Industry: Class II Special Controls Guidance Document—Cord Blood Processing System and Storage Container
- Final Rule: Human Cells, Tissues, and Cellular- and Tissue-Based Products—Donor Screening and Testing and Related Labeling
- Final Rule: Blood Vessels Recovered with Organs and Intended for Use in Organ Transplantation
- Final Rule for Industry: Medical Devices; Hematology and Pathology Devices; Classification of Cord Blood Processing System and Storage Container.

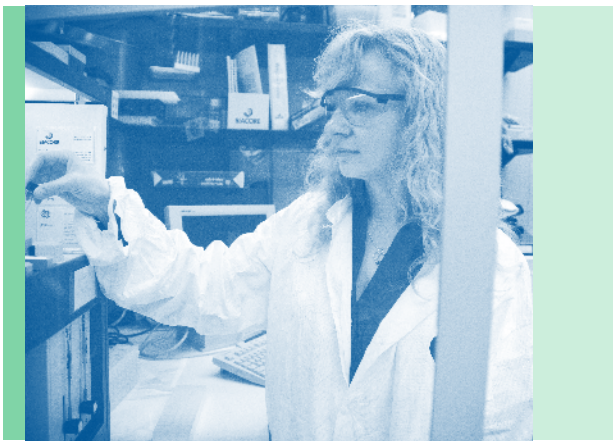
Interdisciplinary Blood Safety Team

One of CBER's ongoing high-priority projects is the development and implementation of an interdisciplinary safety team for blood and blood products. This team was launched in July 2006 to increase safety by enhancing collaboration, coordination, evaluation, and response to complex and emerging blood and blood product safety issues. The Blood Safety Team (BST) also helps identify and implement long-term priorities, innovative practices and collaborations, quality improvement, and communications.

The BST is composed of experts from multiple disciplines, including product manufacturing, safety, clinical, compliance, epidemiology, and communications. This team shares common data and meets on a regular basis to ensure CBER addresses complex blood and blood product issues appropriately and can proactively identify and address significant ongoing and emergent safety issues. The team also evaluates improvements for the acquisition and use of safety information. BST has established communication links among its members and is ready for activation in the event of an emerging situation. The team collaborates with members of ORA, CDC, and other offices and agencies.

In FY 2007, BST achieved the following significant accomplishments:

- Developed a set of goals for the BST, which include:
  - improve response to blood safety issues
  - improve blood safety information quality and availability
  - improve processing of blood safety information
  - enhance external outreach, evaluation, and risk communication
- Contributed to the development and publication of two final rules and seven guidances for industry on blood safety:
  - Final Rule: Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection ("Lookback"); Final Rule
  - Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Direct Final Rule
  - Guidance for Industry: "Lookback" for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV
  - Guidance for Industry: Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes
  - Guidance for Industry: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs
  - Draft Guidance for Industry: "Computer Crossmatch" (Electronic Based Testing for the Compatibility between the Donor's Cell Type and the Recipient's Serum or Plasma Type)
  - Guidance for Industry: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components
  - Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments
  - Guidance for Industry: Bar Code Label Requirements–Questions and Answers
- Evaluated methods to improve collection of adverse events, including transfusion-related fatalities, blood product deviation reports, pathways to track plasma derivatives, and increasing access to healthcare databases
- Investigated several product-related events resulting in enhancements to the public health.



Margaret Mikolajczyk, M.S., Laboratory of Plasma Derivatives, Office of Blood Research and Review, CBER

Fifteen New Blood Typing Tests

On September 14, 2007, CBER licensed 15 new blood typing tests that were previously unavailable in the U.S. These tests, known as blood grouping reagents, are used to determine the blood type of blood donors, an essential step in ensuring safe blood transfusion for patients. If mismatched blood is administered to a patient, it may cause a serious and potentially fatal reaction. To prevent the problem, patients must receive compatible blood based on the results of blood typing tests.

The newly approved ALBAclone Blood Grouping Reagents include the common ABO and Rh tests, plus tests for rare blood types. The reagents are monoclonal antibodies, highly specific antibodies, which ensure product uniformity and availability. Blood grouping reagents are crucial to the provision of compatible blood to patients requiring transfusions.

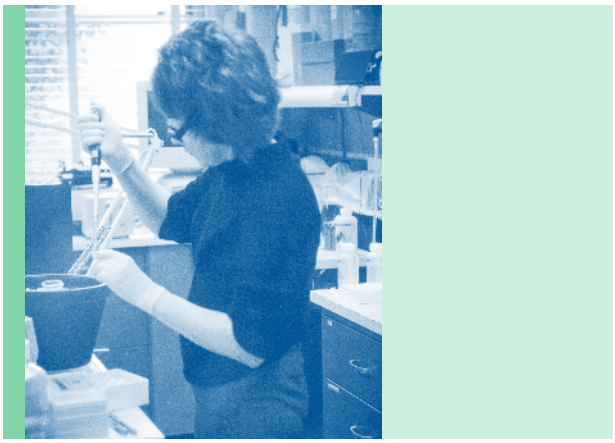
"The licensing of these reagents will provide more choice for blood establishments and transfusion services and may facilitate testing for rare blood groups," said Jesse L. Goodman, M.D., M.P.H. "Licensure of these additional blood grouping reagents will help ensure a more stable supply of these tests, especially important in the event of a product shortage."

First Test to Screen Blood Donors for Chagas Disease

On December 13, 2006, CBER approved the first test to screen blood donors for the blood-borne parasite that causes Chagas disease. The test, called ORTHO T. cruzi ELISA Test System, detects antibodies to the Trypanosoma cruzi (T. cruzi) parasite and is manufactured by Ortho-Clinical Diagnostics, Inc.

As many as 11 million people are currently infected by T. cruzi, most commonly in parts of Mexico and Central and South America, and most of these people have no symptoms or signs of the disease. The infection is usually acquired from the bite of an infected insect, but can also be transmitted through blood transfusions or organ transplants. Early infection is usually mild and unrecognized, persists for life, and can cause organ damage—particularly of the heart and esophagus—causing an estimated 50,000 deaths annually worldwide. Infection can also be severe in people whose immune systems are suppressed, such as organ transplant recipients.

There is increased concern among health agencies over the potential for the transmission of Chagas disease in the U.S. by blood transfusion and organ transplantation because of the increase in the number of U.S. residents who previously lived in countries where the infection is common. The new test identifies infected donors and therefore can reduce the risk of disease transmission through the use of infected blood and organs. In studies reviewed by FDA, the test was found to be accurate 99 percent or more of the time. Since its approval, the test has continued to perform at this level of accuracy with more than 8 million donations screened and 300 cases detected.



Elena Karnaukhova, Ph.D., Laboratory of Biochemistry and Vascular Biology, Office of Blood Research and Review, CBER

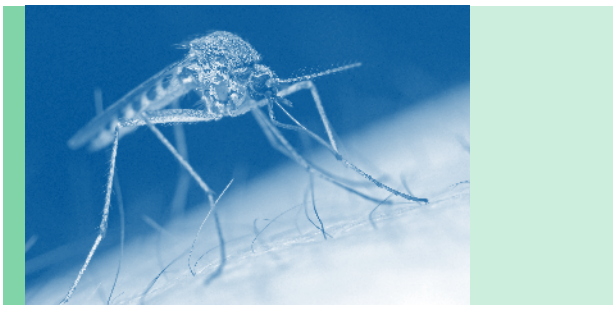
Tests to Screen for West Nile Virus

First Fully Automated Test to Screen for West Nile Virus

On March 2, 2007, CBER approved the first fully automated nucleic acid test to screen for WNV in blood and tissue donors. Manufactured by Chiron, the Procleix WNV Assay on the Procleix TIGRIS System is licensed to detect WNV genetic material in plasma specimens from individual donors of blood, tissue, and organs, and other living donors. It is not intended for use on cord blood specimens or as an aid in the diagnosis of WNV infection.

This assay system can be used for testing individual donor samples or for testing pooled samples from up to 16 individual donations of whole blood and blood components. The Procleix assay system provides flexibility that allows implementation of testing of individual blood donor samples more extensively during periods of high WNV activity.

"The capability of full automation can reduce the potential for human error while accelerating donor



screening and enhancing the safety of blood and tissues," said Jesse L. Goodman, M.D., M.P.H. "This is the latest step forward in what has been a very successful industry-government effort to keep blood safe from the emerging threat of West Nile virus."

WNV is typically spread by infected mosquitoes, but much less commonly, can also be transmitted through blood transfusion or organ transplantation. Although most infected individuals have mild disease and recover spontaneously, infection can be serious or even fatal. WNV was first detected in the U.S. in 1999; since then, it has reoccurred each year, becoming endemic in the country. It is estimated that between 1 and 3 million people have been infected with WNV.

Second West Nile Virus Screening Test

On August 28, 2007, CBER approved the Cobas Taqscreen WNV test, manufactured by Roche Molecular Systems, Inc. The Cobas TaqScreen test is an automated test that detects the genetic material of the virus early in the infection. Testing for nucleic acid improves blood and organ safety by detecting virus in infected donors even before the donor's body has begun to produce antibodies against the virus.

The Cobas TaqScreen WNV test is approved for the detection of the virus in plasma specimens from human donors of whole blood and blood components (plasma, red or white cells, platelets) and living donors of cells, reproductive cells, and other tissues. It is also intended for use in testing plasma specimens of organ donors when specimens are obtained while the donor's heart is still beating. The test is not intended for use on samples of cord blood or as an aid in the diagnosis of WNV infection.

James L. Kenney, D.Sc., Limulus Amebocyte Lysate Laboratory, Office of Vaccine Research and Review, CBER

"This action is the culmination of the dedicated efforts of FDA, our sister agencies, blood establishments, and manufacturers to bring donor screening tests to market for this increasingly common virus," said Jesse L. Goodman, M.D., M.P.H. "As a result, blood centers and hospitals now have a choice of two FDA-approved tests to screen for West Nile Virus in donated blood and organs."

New Test to Diagnose HIV-1 Infection

On October 5, 2006, CBER approved APTIMA HIV-1 RNA Qualitative Assay, the first nucleic acid test (NAT) for the diagnosis of HIV-1 infection. The assay is manufactured by Gen-Probe, Inc.

"This product offers medical diagnostic laboratories the ability to perform a gene-based test for HIV-1 that, until now, was only available as part of a larger kit used to screen blood and plasma donors," said Jay Epstein, M.D., Director of the Office of Blood Research and Review, CBER. "This test also can detect infection with HIV-1 earlier than HIV antibody tests when used to detect primary HIV-1 infection."

This test also offers a potential alternative to the traditional Western blot test that is currently being used to confirm HIV-1 infections when screening tests for HIV-1 are positive. Having an alternative test is important because the Western blot can be difficult to interpret and may not always provide a conclusive result.

First Rapid Test to Screen for Bacterial Contamination in Blood Platelets

On September 18, 2007, CBER cleared for marketing the first rapid test to detect bacterial contamination in blood platelets prior to transfusion. The Platelet Pan Genera Detection (PGD) Test System, developed by Verax Biomedica, Inc., is a disposable test strip for use in hospital-based transfusions as a supplement to current quality control testing by blood establishments following collection of platelets using an automated instrument.

Platelets are used to prevent or treat bleeding in individuals undergoing chemotherapy for cancer, after major trauma, during or after surgery, and to treat individuals who do not produce their own platelets.

Platelets contaminated with bacteria pose a risk of serious and potentially life-threatening bloodstream infection ("blood poisoning") to patients who receive these cells by transfusion. In fact, bacterial contamination of platelets is the leading cause of transfusion-related fatalities due to infections.

Rapid testing of blood platelets using the Platelet PGD Test System permits units of platelets to be retested within 48 hours after donation--at a time closer to

their use. Although the test system is less sensitive than standard cultures, it is done later in storage when bacteria, if present, have multiplied and are present at higher levels that are easier to detect.

Assessing the Potential Risk of variant Creutzfeldt-Jakob Disease from Blood Products

A rare but fatal brain infection called variant Creutzfeldt-Jakob Disease (vCJD) has emerged in recent years as a potential threat to recipients of plasma-derived clotting factors and other plasma-derived products, such as immune globulin and albumin. CBER developed a computer-assisted model for estimating this risk to recipients of plasma-derived clotting factors in order to ensure that both patients and physicians understand this issue. This model was developed to assess the risk of U.S.-licensed, plasma-derived Factor VIII products and a plasma-derived Factor XI manufactured in the United Kingdom and used under IND in a small number of patients in the U.S. between 1989 and 2000. The results of the risk assessments and communication strategies were presented to FDA's Transmissible Spongiform Encephalopathies (TSE) Advisory Committee in September and December 2006.

Based on the risk assessments, the Public Health Service (PHS) believes the risk of vCJD to patients who receive U.S.-licensed, plasma-derived Factor VIII products is extremely small, although PHS does not know the risk with certainty. vCJD risk from other U.S.-licensed, plasma-derived products, including Factor IX, is likely to be as small or smaller. Additionally, the PHS believes the potential risk of vCJD infection from plasma-derived Factor XI, although not known for certain, is likely to be small.

Furthermore, CBER developed and implemented a risk communication plan in order to ensure the findings of the risk assessments reached the appropriate stakeholders. CBER partnered with patient advocates and risk communication experts to develop educational materials and arranged for hemophilia treatment centers and professional and advocacy organizations to publicize the findings through newsletters and other media. Finally, CBER launched a web page (http://www.fda.gov/cber/blood/vcjdrisk.htm) that provides the risk assessments and risk communication materials. Additional links are provided to FDA's current guidance documents on deferral of blood and plasma donors who may be at increased risk of vCJD and to other sources of information on vCJD.

Interdisciplinary Vaccine Safety Team[60]

CBER launched a multidisciplinary Vaccine Safety Team (VST) in FY 2007 to enhance collaboration, coordination, evaluation, and responses to complex and emerging vaccine safety issues.

The VST comprises experts in product manufacturing, safety, clinical trials, compliance, epidemiology, and communications. The team shares data and meets on a regular basis to address complex vaccine issues; proactively identifies and addresses significant ongoing and emergent safety issues; and determines how to improve the acquisition and use of safety information. In addition, the team is ready for activation in the event of a threat to vaccine safety.

This multidisciplinary approach to early detection, analysis, action, and communication facilitates information-sharing and analysis of vaccine problems. This includes collaboration with ORA, CDC, and other offices and agencies throughout the entire product life cycle. The VST also helps to identify and implement long-term priorities, innovative practices and collaborations, quality improvement, and communications.

In FY 2007, VST achieved the following significant accomplishments:

- Implemented standard operating procedures
- Identified safety gaps and assisted in safety issues, such as reports of anaphylaxis in Canadians with the measles-mumps-rubella vaccine (MMRII).
- Contributed to the development and publication of "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

PATIENT AND CONSUMER SAFETY

Adverse Event Monitoring[61-71]

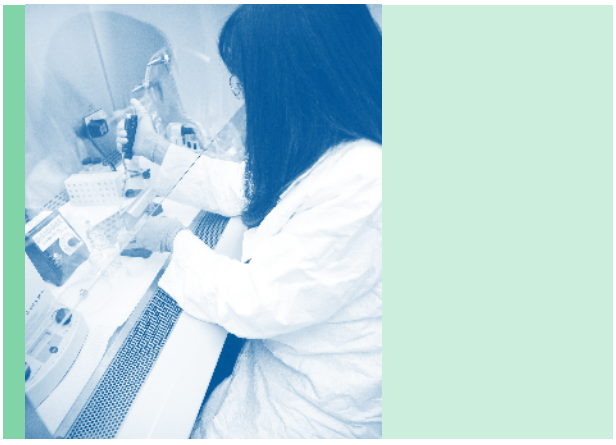
In addition to establishing product safety teams in 2007, CBER established a quantitative risk assessment unit to address more mathematically complex product and public health safety issues. CBER undertook a quantitative assessment of risks of vCJD transmission through plasma-derived Factor VIII products and discussed the risk assessment and communication strategies at the Transmissible Spongiform Encephalopathies (TSE) Advisory Committee meetings in September and December 2006.

The Vaccine Adverse Event Reporting System (VAERS), jointly managed by CDC and CBER is a passive postmarketing safety surveillance program that collects information about adverse events (suspected side effects) that might be linked to use of U.S.-licensed vaccines. CBER also collaborates with CDC on select hypothesis testing studies in the Vaccine Safety Datalink (VSD), a large, linked database for active monitoring and analysis of vaccine safety. In addition, CBER undertook a Medicare data analysis project that helps to fill an important gap in vaccine safety hypothesis testing, since other databases may not have sufficient statistical power to examine rare events and can under-represent the elderly.

The Adverse Event Reporting System (AERS) is a computerized information database designed to support FDA's postmarketing safety surveillance program for all approved drugs and therapeutic biologic products. FDA receives suspected adverse drug reaction reports from manufacturers as required by regulation. Clinical reviewers in CDER and CBER evaluate the reports to monitor drug safety, watch for evidence of safety signals and initiate further epidemiological studies when appropriate.

During FY 2007, CBER, in collaboration with CDC and Harvard University, initiated the influenza vaccine safety surveillance healthcare database project. This new initiative is a pilot program using other databases to assess rapidly and prospectively the safety of seasonal flu vaccines in preparation for tracking adverse effects of pandemic vaccines if and when they are used.

During FY 2007, CBER cooperated with the DHHS National Vaccine Program, NIH, CDC, and the Health Resources and Services Administration to plan and hold a major public workshop entitled "Vaccine Safety Evaluation: Postmarketing Surveillance."



Maria Rios, Ph.D., Laboratory of Molecular Virology, Office of Blood Research and Review, CBER

Blood and Blood Product Safety and Availability

Risk-based Compliance Program Implemented for Inspections of Source Plasma Establishments

On October 1, 2006, CBER implemented a revised Compliance Program for inspections of Source Plasma

establishments, which utilizes a risk-based approach involving two inspection options for Level 1 and Level 2 inspections. Thirty one new establishments that collect Source Plasma were opened in FY 2007 to expand the supply of plasma derivatives (e.g., clotting factors and immunoglobulins).

A Level 1 inspection is a comprehensive, systems-wide evaluation of the establishment's compliance. A Level 2 inspection is a streamlined evaluation of an establishment's compliance when the facility has already met certain criteria. In addition to incorporating a risk-based approach, the revision also included an updated list of references, guidance documents, and program contacts, as well as other minor editorial changes to provide consistency with other Compliance Programs.

Workshop on Immune Globulins for Primary Immune Deficiency Diseases

On April 25–26, 2007, CBER held a public workshop on immune globulins for primary immune deficiency diseases (PIDD). The workshop was co-sponsored by the DHHS Office of the Secretary/Office of Public Health and Science, the Immune Deficiency Foundation, and the Plasma Protein Therapeutics Association.

Leading clinical immunologists, industry representatives, and patient advocates joined government experts to discuss ways to identify the antibodies most likely to prevent infections in patients with PIDD, and current and potential potency tests for immune globulins, especially in the cases of H. influenzae and S. pneumoniae. To determine if these antibody specificities would also be useful and relevant to ensure lot-to-lot manufacturing consistency, participants supported the need to design and implement testing protocols to assess levels of binding and functional antibodies in such immune globulin products.

The public workshop also included a discussion about the declining measles antibody levels in U.S.-licensed immune globulins and the potential clinical impact on patients with PIDD. Measles antibody levels are currently a standard lot release measure of potency in U.S. immune globulins; however, declining antibody levels have been observed in products over the past several years because of the decline of measles titers in the donor population.

Following the workshop, the topic of measles antibody levels in U.S.-licensed immune globulin products was discussed at the August 2007 Blood Products Advisory Committee meeting. CBER is currently gathering data to correlate product titer levels to patient trough levels and estimated protective levels, to address diminishing measles antibody titers in immune globulin products.

Assessment of Threat to Blood Supply from Emerging Infectious Diseases

Malaria

Malaria occurs in more than 100 countries, causing a total of approximately 500 million infections and 2 millions deaths annually. Each year, more than 28 million Americans travel to or live in countries where malaria is transmitted. Travelers and immigrants from these malaria-endemic countries pose a potential risk of passing the infection to others through blood transfusion.

Currently, there is no FDA-licensed blood screening test to detect the presence of malaria parasites. Therefore, FDA has recommended donor deferral policies based on travel to malarial areas or residence history to minimize the risk of transfusion-transmitted malaria (TTM). The agency estimates approximately 120,000 donors are deferred each year because of the potential risk of exposure to malaria parasites.

In order to minimize the number of deferred donors, CBER is working to develop laboratory tests to detect malaria parasites in blood donors. Such tests might further improve the blood safety from the risk of TTM and reduce the unnecessary deferral of otherwise suitable donors. A secondary objective is to conduct research on malaria immunology and pathogenesis

Robert Duncan, Ph.D., Laboratory of Bacterial, Parasitic and Unconventional Agents, Office of Blood Research and Review, CBER

to discover biomarkers of protective immunity and virulence. CBER is also working to develop laboratory tests (based on genetic markers) that could set a standard for preclinical evaluation of the safety and efficacy of malaria vaccines.

Babesiosis

Babesiosis, a malaria-like illness, is caused by infection of erythrocytes with several species of parasitic protozoans of genus Babesia. The highest prevalence of babesiosis (both naturally occurring and transfusion-induced) occurs in the U.S., where the disease is most prevalent in the Northeastern states, Midwest, and in parts of Texas and California. Transfusion-transmitted babesiosis (TTB) caused by the use of blood and blood products collected from a donor with an asymptomatic Babesia infection presents a serious challenge for blood safety in endemic states. There is no FDA-approved test to detect babesia infections in patients or in blood donors.

During the last 40 years, more than 60 incidents of TTB have been reported in the U.S. Five cases of fatal TTB (primary or contributory cause of death) were reported to FDA in 2006–2007. These cases represent an unexpected rise in the incidence of TTB. Therefore, CBER has initiated a research project to develop sensitive, DNA-based tests for detecting Babesia infections in blood donors.

Leishmania

In 2003, FDA supported a lifetime deferral of potential blood donors who were diagnosed with leishmaniasis and a one-year deferral of donors for travel to Iraq in order to reduce the risk of transmission-based leishmaniasis. Since that time, thousands of people have traveled to or served in Iraq and returned to the U.S., and the prevalence of infection among these individuals remains uncertain. To address these issues, CBER scientists in collaboration with scientists at Walter Reed Army Institute of Research are evaluating new approaches to more sensitive detection of Leishmania in blood.

Vaccines

Vaccine Clinical Trial Safety Monitoring and Assessment Programs

Because preventive vaccines are usually developed to prevent disease in a healthy population, there is a very low tolerance of risk. To help industry develop their clinical trial safety monitoring and assessment programs, CBER released a final guidance for industry in September 2007: "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." This guidance provides a grading system for the severity of clinical and laboratory abnormalities in clinical trial participants; and, therefore might also help investigators establish rules for halting a particular study because of adverse events.

Development of Group A Streptococcal Vaccines: Workshop to Assess Laboratory Methods to Foster Development of Vaccines

On August 25–27, 2007, CBER participated in a workshop hosted by NIAID on Group A streptococcal laboratory methods that focused on vaccine-related issues. Participants of this workshop, which was designed to reinvigorate interest in these illnesses, reviewed laboratory methods for surveillance and measurement of immune responses to support vaccine development.

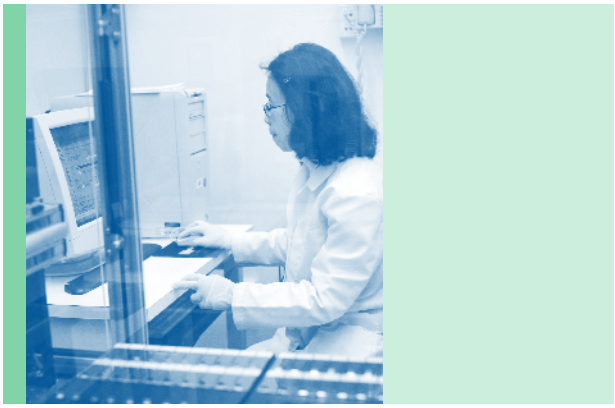
CBER reviewed its efforts to facilitate the development of these vaccines and provided expertise on improving the assays. International streptococcal experts further discussed the status of these assays and related reagents, as well as how these assays could be used as immune correlates of protection and surrogates for the licensure of Group A streptococcal vaccines.

Cell, Gene, and Tissue Therapies

Critical Path Activities to Improve the Safety and Efficacy of Human Cells, Tissues, and Cellular- and Tissue-Based Products

CBER researchers are trying to discover the causes of certain gene therapy adverse events, especially those linked to adenoviral and retroviral vectors, which are among those most commonly used for gene therapy.

The adenoviral vector adverse events research aims to clarify the interaction of these vectors with cells. The retroviral vector research, which is being done in collaboration with National Institute of Environmental Health Sciences as part of the National Toxicology Program, is investigating the risk of insertional mutagenesis. Included in this collaboration are preclinical studies involving DNA-based therapeutics, specifically focusing on reducing the risk of retroviral-mediated tumorigenesis in humans. The goals of the project are to reduce the uncertainty in the risk assessment/risk-benefit analysis; enable a better estimate of risk; and establish high-quality, science-based safety assessments/risk management decisions for the consumer.



Amy X Yang, Ph.D., Tumor Vaccine and Biotechnology Branch Office of Cellular, Tissue and Gene Therapies, CBER

Policy for Long-Term Follow-up of Subjects in Gene Therapy Clinical Trials

Participants of gene therapy clinical trials who are exposed to gene therapy vectors can be at risk of delayed adverse events due to the persistent biological activity of the genetic material or other components of the products used to carry the genetic material.

In response to this potential complication, CBER published in November 2006, the Guidance for Industry "Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events." This guidance, which covers long-term follow-up (LTFU) for adverse events in participants in gene transfer clinical trials for delayed adverse events, provides practical options for the collection of LTFU data that could be used to improve such studies.

The gene therapy community has responded favorably to the release of this guidance. This approach to LTFU will provide CBER, clinical investigators, and IND sponsors important information on potential risks associated with gene therapy vectors and gene transfer clinical trials.

Guidances for Cell, Tissue, and Gene Therapies

To communicate our regulatory expectations to industry and academic researchers, CBER issued the following guidances in 2007:

- Final Guidance to Industry: "Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events"
- Draft Guidance for Industry: "Minimally Manipulated, Unrelated, Allogeneic Placental/ Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies"
- Draft Guidance for Industry: "Cell Selection Devices for Point-of-Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells"
- Draft Guidance for Industry: "Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage".

Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group Strategic Plan

CBER staff participate in the MATES Interagency Working Group, organized under the auspices of the Subcommittee on Biotechnology, National Science and Technology Council (NSTC). The primary goal of MATES is to facilitate communication across departments/ agencies by regularly exchanging information and enhancing cooperation through co-sponsorship of scientific meetings and workshops. In June 2007, the MATES working group published a document entitled "Advancing Tissue Science and Engineering: Foundation for the Future." This document provides a strategic plan for the advancement of TE in the Federal government. CBER has met with product manufacturers currently developing these innovative products and has a unique perspective on issues associated with tissue-engineered product development.

Workshop on "Bringing Therapeutic Cancer Vaccines and Immunotherapies through Development to Licensure"

On February 8–9, 2007, CBER and the National Cancer Institute (NCI) co-sponsored a highly successful, two-day public workshop on cancer vaccines and immunotherapy. This workshop was an important and timely outreach activity to stakeholders in the field of therapeutic cancer vaccines. Participants and attendees included researchers and representatives of biotechnology and pharmaceutical companies who are involved in product development and preparation for licensure.

Participants gained important insights into the efficient development of cancer vaccines and how to avoid pitfalls. The workshop also enabled industry to provide feedback to regulatory agencies.

In addition, this workshop was an excellent example of interagency collaboration between FDA and NCI, and with the American Association for Cancer Research, the American Association of Immunologists, the Cancer Vaccine Consortium, the International Association for Biologicals, and the International Society for Biological Therapy of Cancer.

Christine Anderson, M.S., Lyophilization Laboratory, Office of Vaccine Research and Review, CBER

Cellular and Gene Therapies: Outreach and Partnerships

CBER provides proactive scientific and regulatory guidance in the areas of novel product development. The Center encourages dialogue with stakeholders on cutting-edge product development to help define the best scientific approaches and reduce product development time and risk. Early and continuing interactions with stakeholders, including the public, have proven to be an effective means of communicating and addressing issues regarding potential risks and benefits, thus avoiding unnecessary regulatory burdens.

CBER staff participated in a variety of collaborative

Manju Joshi, Ph.D., Single Radial Immunodiffusion Laboratory, Office of Vaccine Research and Review, CBER

meetings during the past fiscal year, such as:

- Attendance at the Cell Therapy/FDA Liaison Meetings to hear industry perspectives on importation of cellular products and minimally manipulated, unrelated allogeneic umbilical/placental cord blood
- First liaison meeting with the American Association of Tissue Banks (AATB), which addressed import and export of HCT/Ps and tissue tracking and recalls. CBER staff also served as liaisons to cell and tissue establishment accrediting and standards-setting organizations, including the AATB standards committee and the American Association of Blood Banks Cellular Therapy Standards Program unit
- Workshop on Accelerating Anticancer Agent Development and Validation co-sponsored by FDA, NCI, AACR and Duke University
- Participation as an Organizing Committee member for the NCI/FDA/industry workshop on Clinical Use of Biomarkers.

Proposed Rule Barring Certain Cattle Material from Medical Products as a Bovine Spongiform Encephalopathy Safeguard

On January 11, 2007, FDA proposed restrictions on certain materials used in medical products to keep them free of the agent thought to cause bovine spongiform encephalopathy (BSE), also known as Mad Cow disease. This is the latest in a series of BSE safeguards that would bar material that has been found to harbor the highest concentrations of this fatal agent in infected cattle.

The proposed rule covers drugs (prescription, over-the-counter, and homeopathic), biologics (e.g., vaccines), and medical devices intended for use in humans, as well as drugs intended for use in ruminant animals (e.g., cattle and sheep). Mad cow disease afflicts cattle.

To ensure companies comply with these prohibitions, FDA proposes a requirement that records be kept to demonstrate that any cattle material used as an ingredient in these medical products or as part of their manufacturing process are not derived from suspect animals.

Convincing evidence has accumulated since 1996 for a causal relationship between mad cow disease in Europe and vCJD in humans. Both disorders, which are thought to be caused by a transmissible agent, are invariably fatal brain diseases, with incubation periods typically measured in years. Transmission of the BSE agent to humans is believed to occur through ingestion of cattle products contaminated with the BSE agent; however, the specific products associated with this transmission are unknown.

CBER INITIATIVES

Values and Vision: Investing in Ourselves

On September 19, 2007, the Commissioner conducted a live broadcast to present feedback from Agency employees on the FDA Values and Vision Initiative. This initiative is the result of assessing the feedback from the 2006 Human Capital Survey that addresses the many challenges FDA faces concerning our internal processes, scientific outcomes, and public perceptions. The survey was sent to all FDA employees for input.

As a result of the 2006 Federal Human Capital Survey, the Agency formed a working group comprising of representatives from the Centers, ORA, and the Office of the Commissioner. Three representatives from CBER participate on this group. The working group conducted 19 focus groups comprised of managers and non-managers at the Centers, field offices, and headquarters. Based on these discussions about survey results, the working group recognized themes and consistent values that emerged from this diverse workforce. The working group then developed a draft Values Statement incorporating six clear operating principles.

Values Statement

We, the U.S. Food and Drug Administration (FDA), protect and promote the health of all Americans by ensuring the safety of foods, cosmetics, drugs, biologics, and medical devices. We are committed to excellence in our mission and maintaining the public trust. In pursuing our mission, we adhere to six fundamental core values. These core values govern our deliberations, decisions, and actions, and provide the framework for our interactions within FDA and with the public and other FDA stakeholders.

Integrity
As stewards of the public trust, we demonstrate the highest standards of ethical conduct and act honestly and with integrity. As a science-led agency, we abide by these principles in formulating, conducting, and presenting research, and in reviewing submissions to FDA. We value and encourage feedback and the use of other tools to allow us to continue to improve our regulatory processes and our interactions.

Excellence
We are a world-class public health regulatory agency. We continually improve our skills and competencies in all matters of public health. We take pride in doing accurate, precise, and timely review, research, and enforcement activity. We work creatively and constructively to improve our policies, procedures, and work products, giving the American public the protection that it requires for the products we regulate with the resources we are given.

Accountability
Consistent with our strong commitment to public service, we maintain the highest degree of individual and professional accountability in the conduct of our work and to those who depend on our expertise. On an ongoing basis, we openly monitor our processes and performance to ensure we continue to do what works well and actively address those areas where we can improve and grow. We value collaboration, teamwork, and providing exemplary customer service. Through the principle of "shared leadership," which is defined as a sense of collective responsibility, we hold each other accountable, irrespective of our position in the Agency.

Equity
Our greatest asset is a talented and committed workforce. We recognize the inherent dignity of every FDA employee and treat each other with civility and respect. We maintain a fair and equitable work environment free from discrimination and harassment of any kind. Conflict in the workplace is inevitable and a sign of health for groups to gain the benefits of multiple perspectives. When properly managed, conflict is an opportunity for creative and constructive dialogue and outcomes. We support open dialogue and early conflict resolution. Under no circumstances do we tolerate discrimination in the workplace.

Diversity
We value diversity in its broadest context, including physical, social, cultural, cognitive, and philosophical perspectives. To be a premier scientific public service agency, we tap into the diverse intellectual capital of many cultures and empower all individuals to contribute to their optimum potential knowing that the highest

performance outcomes emanate from diversity of thought. We encourage open debate and value constructive dissent to improve our decision-making. We embrace both the moral and business imperatives for diversity in our workforce and all of our operations.

Transparency

We maintain our integrity through openness and transparency of our regulatory processes. While observing regulatory requirements preventing disclosure of certain information, we communicate openly with our internal and external stakeholders, including our workforce, the public, industry, academia, Congress, and our international partners. We encourage openness and transparency in our decision-making related to enforcement, product review, and regulatory activities. Our regulatory decisions are supported by a clear administrative record, scientific and policy justifications, risk assessments, and technical information materials provided in a format reasonably understandable to the lay public. We use a variety of measures—including notice and comment rulemaking, issuing guidance documents with the opportunity for comment, public meetings and hearings, community outreach, and education—to promote awareness, cultivate trust, and engage people in our processes.

CBER's leadership supports the Vision and Values Initiative, and will continue to develop the important steps taken in 2007.

User Fees

Prescription Drug User Fee Act

In 1992, Congress passed Prescription Drug User Fee Act. Congress subsequently reauthorized PDUFA three times: first, in the FDA Modernization Act of 1997, then in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, and most recently in FDAAA. PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a company seeks FDA approval for a new drug or biologic prior to marketing, the company must submit an application along with a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed.

PDUFA has provided FDA with needed resources for the review of human drug and biologic applications. Fees are used to help reduce the time required for evaluating human drug applications and to support review quality. FDA submits annual performance and financial reports to Congress on progress in streamlining the drug review process and use of PDUFA fees.

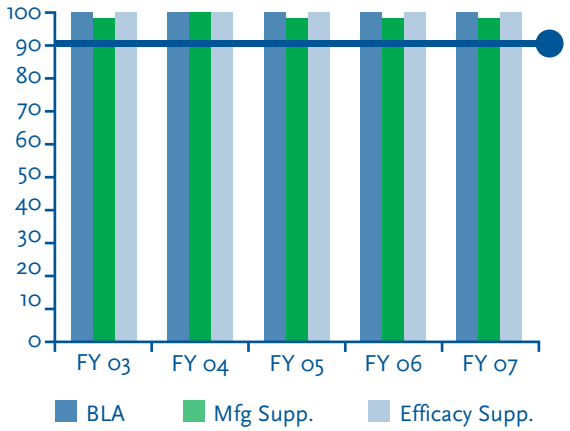
Medical Device User Fee Modernization Act

The Medical Device User Fee and Modernization Act of 2002, Public Law 107-250, amended the Federal Food, Drug, and Cosmetic Act to provide the FDA important

CBER User Fee Review Performance

License Application and Supplements

% of First Actions Within Goal* for Cohort Fiscal Years 2001-2005



*PDUFA Performance Goal: 90% Data through 9/30/06 (525bp) RIMS:04.14.06

responsibilities, resources, and challenges. MDUFMA was signed into law on October 26, 2002. The program was reauthorized in the Food and Drug Administration Amendments Act of 2007 (FDAAA) as the Medical Device User Fee Act (MDUFA).

MDUFA provides needed funds to FDA for "the review of devices and the assurance of device safety and effectiveness so that statutorily mandated deadlines may be met." MDUFA user fees coupled with the additional appropriated resources have provided the following benefits:

- safe and effective devices used to diagnose and treat disease are reaching the public more rapidly
- manufacturers are receiving timely, high-quality application reviews
- devices marketed in the U.S. continue to meet high standards for safety and effectiveness.

FDA Amendments Act

On Sept. 27, 2007, the President signed into law the Food and Drug Administration Amendments Act (FDAAA) of 2007. This law contains amendments, adds many new provisions and reauthorized some existing provisions to the FD&C Act. The existing laws pertaining to PDUFA and MDUFMA were set to expire on September 30, 2007. FDAAA reauthorizes the PDUFA and MDUFMA programs for five years. These changes and new amendments provide important resources and strength to the agency's ability and commitment to safeguard and advance public health. Titles of the new amendments impacting on CBER include the following:

Title I

PDUFA/CBER—CBER's continued success in PDUFA is reinforced by additional revenues to support the growing postmarket activities related to safety after approvals. These resources enable CBER to increase personnel and expand postmarket activities. Previously, the legislation restricted the allocation of PDUFA fees beyond a 3-year window, after approval, to any postmarket activity.

CBER 510k Average Review Time
Receipt to Final Action
FY 2002-FY2006

	FY02	FY03	FY04	FY05	FY06	FY07
CBER Review Time (days)	114.0	57.1	64.6	68.5	63.3	63.1
Average Number of Cycles	1.7	1.3	1.4	1.5	1.1	1.4

Includes SEs/NSEs/WDs
Data through March 31, 2006

Additionally, the workload adjustment provision was improved to better account for work performed prior to the NDA or BLA submission. These resources will continue to enhance the premarket activities and provide CBER with additional personnel.

PDUFA fee revenues were also planned to support the costs of the future relocation of the personnel in CBER to FDA White Oak campus in FY 2012. Infrastructure costs preceding the move and the actual move costs of personnel are planned.

Title II
MDUFMA/CBER—The Act provides enhanced resources to support the review of medical device products with biologic components. The unintended consequences of the cycle goals in the previous act resulted in a significant change for the new provisions of MDUFMA. These goals include interactive review of medical device applications. Fee resources to continue the MDUFMA review are annually increased to cover any erosion of pay, benefits, and other supporting costs.

Title III
Pediatric Medical Device Safety and Improvement Act—This Act will require applicants to provide information on pediatric subpopulations and provide the number of affected pediatric patients.

Title IV
Pediatric Research Equity Act—Pediatric studies are required when submitting an application or supplement for a new active ingredient, indication, dosage form, dosing regimen, or route of administration. Applicants must assess safety and effectiveness for the claimed indication in relevant pediatric populations using age-appropriate formulations. CBER participates in the Pediatric Review Committee, established by FDA, that is comprised of experts in pediatrics, biopharmacology, statistics, chemistry, legal issues, pediatric ethics, and others as appropriate.

Title VII
Advisory Committee— Advisory Committee - Regarding conflict of interest provisions, there are many changes as a result of this new legislation. For example, there is a cap on the number of waivers permitted, and all waivers must be made public.

Title VIII
Clinical Trial Database—The title expands clinical trial registry responsibilities and adds results to the database. The primary responsibility is for NIH to implement; however, there are significant FDA directives and actions. There are many timelines noted that FDA needs to work in concert with NIH to implement.

Title IX
Enhanced Authorities Regarding Postmarket Safety of Drugs and Biologics—The title provides FDA with new authorities for FDA to require postmarket epidemiologic studies and clinical trials and requires sponsors to make safety-related labeling changes and to develop and comply with Risk Evaluation and Mitigation Strategies.

Title XI
Encourage Treatments for Tropical DiseasesThis title encourages sponsors to submit human drug applications for treating tropical and other infectious diseases for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary. The title directs the Secretary of Health and Human Services to develop a priority review program for evaluating tropical disease product applications.

The senior management for the Center, as well as the Agency, has generated working groups to ensure compliance with the intent of the legislation.

Management Initiatives

CBER Research Management Initiative

CBER implemented the Research Management Initiative to develop a portfolio of regulatory research priorities and metrics for individual program evaluation in order to establish a consistent and transparent process for prioritizing research. As a part of this initiative, in FY 2007, CBER is implementing a new research planning, management, stakeholder input and evaluation system. Implementation of this initiative includes reviewing the FY 2007 workload, updating research priorities and reporting on research proposals, and rating the programs.

Employee and Leadership Development

CBER developed a draft policy and procedure to implement Individual Learning Accounts, a designated amount of money that is set aside for use by a CBER employee and centrally managed in an account established by using appropriated funds allocated to the Agency. These funds may be used only for education, training, and career development activities relevant to the employee's federal employment that have been approved, in advance, by the employee's supervisor. The program was set to be implemented in FY 2008.

In support of succession planning, CBER implemented and enrolled 28 staff in a Leadership for Non-Supervisors program that includes seven training events and a developmental leadership assignment.

In 2007, CBER accomplished the following goals:

- Implemented a mentoring program with 14 mentoring pairs
- Supported 22 staff in professional development activities at academic and clinical organizations
- Completed 64 internal training events, with more than 1,200 staff attending
- Supported 53 staff attending FDA Science Symposium
- Supported 236 staff attending external meeting, workshops, and conferences
- Developed a coaching program for supervisors and managers.

Quality Assurance

CBER staff engage in dispute resolution and provide an objective resource for the ongoing review and evaluation of Center programs and operations.

The Center is committed to ensuring quality in the performance of all core functions; and is performing a variety of quality assurance activities for many of its research, review, and compliance activities. CBER also monitors implementation and the impact of changes in the Managed Review Process and provides an ongoing evaluation of its efforts to meet PDUFA performance goals for specific product categories.

In FY 2007, as part of CBER's ongoing quality assurance efforts, the Center held four Clinical Hold Oversight Committee meetings. In addition, the CBER pilot program to automate internal auditing of administrative activities associated with completed action files, which was initiated in FY 2006, continues to track the progress toward a goal of accurate and timely filing of all completed action files.

The Laboratory Quality System Team and office quality managers and laboratory quality system staff continued to lead the Center's efforts to gain laboratory accreditation. In FY 2007 the team managed a CBER/CDER collaborative contract for laboratory quality system development that included the development, approval, and release of procedures and work instructions to support document control, equipment maintenance and calibration, training, and competency documentation.

CBER staff have also standardized the coordination of lot release and related testing activities with the Managed Review process; and generated, reviewed, and approved product testing plans for many CBER-regulated products. Training procedures for these plans are completed for some products and underway for others. CBER anticipates this laboratory accreditation effort will continue throughout FY 2008.

In addition, the Center Laboratory Quality Manager works with the Quality Resource and Guidance Team—a subcommittee to the FDA Management Council that is providing guidance on the internal application of quality systems—and in the PDUFA Quality System Group, which oversees use of PDUFA funds to support quality systems within FDA.

The Quality Assurance Staff (QAS) assisted in preparations for a WHO assessment of CBER, participated in the assessment process, and assisted in CBER's response activities (see International section for additional details). The QAS is also participating in the implementation of the Quality Management Plan for the CMC discipline of the Managed Review Process (see Managed Review Process section for additional details).

As part of its internal review process, CBER's Ombudsman investigates and responds to complaints about the CBER regulatory review processes and provides for informal formal dispute resolution.

In FY 2007, CBER received approximately three informal requests per week for assistance, primarily from outside FDA. No formal dispute resolution requests were received. Of the informal requests, 21 required a substantial level of intervention or mediation and two originated within FDA.

In addition, the CBER Ombudsman handles questions about inter- and intracenter product jurisdiction and serves as a member of the Tissue Reference Group. With respect to intercenter jurisdiction in FY 2007,

more than 70 Requests for Designations were received, of which 21 were specifically assigned to CBER for evaluation. Many of these concerned combination products that included a biologic and device, biologic and drug, or drug and device component. Informal jurisdiction questions received from inside and outside FDA averaged five to ten per month.

Communications

CBER is committed to effective and timely communication. Such communication is a key principle to enhancing the capabilities of health professionals and the public by providing important information on the benefits, risks, and safe use of our products.

As medical products and medical science become increasingly complex and healthcare providers may need to choose among a variety of treatment options, we have tried to provide better access to clear and timely risk-benefit information. For example, in February 2007, CBER issued a public health notification concerning RotaTeq, a vaccine to prevent rotavirus in infants and children. This notification conveyed information to the public concerning reports of cases of a serious adverse event received postmarketing, encouraged healthcare providers to report additional cases to us, and recommended that parents contact their child's health care provider if their child had signs or symptoms of intussusception.

Subsequently, CBER released an explanatory communication to make healthcare professionals and consumers aware of new information added to the labeling, while reiterating that indications and use of RotaTeq did not change, that no new or revised warnings or precautions were issued, and that the available data support the safety and effectiveness of the vaccine.

CBER enhanced its ability to handle media work on this and other matters through a collaborative project in which the Agency's Office of Public Affairs (OPA) and OCTMA established protocols for proactively and effectively communicating information to the media. This included facilitating, often in conjunction with OPA, numerous responses to media inquiries and media interviews of CBER personnel. OCTMA identified important opportunities to highlight Center and Agency activities and issued press releases related to product approval and Center activities. For example, the collaborative approach facilitated CBER's efforts to inform the general public, our stakeholders, and Agency personnel of the ongoing progress in the reauthorization of user fee acts.

During FY 2007, the Center replied to approximately 3,000 inquiries from consumers, healthcare providers, nongovernmental organizations, and other nonregulated entities, as well as an additional 2,000 inquiries from industry. CBER routinely responds to the following requests for information:

- Congressional requests for information and oversight requests
- Reviews of testimonies and responses to hearing issues prepared by other agencies
- Information needed for Congressional briefings on pertinent FDA issues
- Information for Congressional hearing preparations, technical assistance, and review of Congressional bills
- Requests from the DHHS Office of the Inspector General and the Government Accountability Office.

Scientific Fellowship Program

CBER is committed to hiring interns and fellows, and providing the needed training to support their development. CBER has a strong commitment to training for all staff, as it is vital for succession planning, bringing new techniques and emerging science into the Agency, and helping build skills needed for implementing regulatory oversight of medical product development and post-marketing surveillance.

Fellowships and internships also provide a flexible mechanism for the temporary employment and professional development of promising research scientists, as well as an alternative employment mechanism to secure the services of proven, talented employees for a period of limited duration. The time spent with the Agency promotes understanding of emerging science and attracts young scientists to CBER, while increasing the range and depth of collaborations between CBER and the outside scientific community. These collaborations are especially helpful for Critical Path projects aimed at facilitating the development of innovative products and providing knowledge that may enhance the safety and effectiveness of medical products.

CBER has also actively recruited underrepresented members of the workforce by participating in the summer internship programs that offer access to students from the Hispanic Association of Colleges and Universities, Historically Black Colleges and Universities, the Workforce Recruitment Program for College Students with Disabilities, and the Washington Internships for Native Students.

Review Management Improvement Initiatives

CBER continues to coordinate and lead multiple review activities aimed at harmonizing business processes and databases, and is actively improving its own review processes for biologics, drugs, and devices, and their associated IT support. These efforts also include initiatives to harmonize business processes across the Agency, the Department, and other Centers, especially CDER and CDRH. CBER Review Management staff continually work to facilitate the implementation of these processes and harmonization through multiple venues, including Center coordinating committees (Review Management Coordinating Committee; Chemistry, Manufacturing, and Controls Coordinating Committee; Standards Management Coordinating Committee; and Information Management Coordinating Committee) led by Review Management staff.

Agency Bioinformatics Harmonization

CBER works to harmonize bioinformatics by participating in the FDA Bioinformatics Board, which was established by the Agency's senior management in February 2006. The Board oversees the planning and management of FDA's bioinformatics activities and ensures communication to all levels of the Agency. CBER staff serve in various capacities on the Board and all subcommittees (Business Review Boards), including the Data Standards Development Lead for the Postmarket Review Board.

Review Management activities critical to the efforts of the Product Quality and Compliance Business Review Board include development of electronic registration and listing systems to establish a harmonized inventory of FDA-related entities (facilities, firms, points of contact, products, and components/ingredients). Key to the success of electronic product listing is the submission of product information using Structured Product Labeling (SPL) and electronic coding of data elements. Review Management staff have taken a lead role in ensuring CBER products can be effectively listed electronically by working on enhancing review capacity for labeling in SPL format.

Quality Systems

CBER is also working closely with the Agency to develop Quality Systems within the Agency and the Center. In coordination with CDER, CBER developed a quality system for Chemistry, Manufacturing, and Controls (CMC) review. In addition, CBER revised our standard operating procedure on meetings, SOPP 8101.1 Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants to incorporate elements of the quality system, and we developed a training program. Review of current CMC practices was initiated, and several areas were targeted for improvement. Both of these initiatives are lead by Review Management Staff, which are active in the FDA Quality Systems Resource and Training Group.

Electronic Standards

CBER is actively engaged in Agency electronic standards development work that include FDA Data Standards Council and its subgroups, the Adverse Event Workgroup (chair) and the Health Level Seven (HL7) Regulated Product Submission (RPS) Standard Group (CBER lead and project coordinator).

The purpose of the RPS standard is to develop a comprehensive set of headings and hierarchy for the information contained in all Agency product applications that will facilitate review procedures. The HL7 group approved RPS Release 1 in May 2007 and the standard will be piloted in the Agency throughout 2008. The standard is based on the Common Technical Document developed by the Center for Drug Evaluation and Research (CDER) and CBER at the International Conference on Harmonization (ICH). FDA expects to continue testing with industry input over the next year with specific emphasis on device and combination product submissions.

The DHHS HL7 Patient Safety Special Interest Group (co-chair) initiative provides leadership in the creation of HL7 patient safety and public health reporting messaging standards, including Individual Case Safety Report (ICSR) and Generic Patient Safety Incident Notification message standards. The FDA plans on adopting the ICSR Release 2 Draft Standard for Trial Use (DSTU) that was approved by HL7 in January 2007. The Agency will use the standard to support an initiative to create a consolidated adverse event reporting portal and data repository for MedWATCHPlus. This effort will improve the quality of direct reports from consumers, healthcare providers, and regulated industry by using a standardized electronic reporting format for all FDA-regulated products. FDA will conduct ICSR DSTU testing throughout 2008. The ICSR is also currently under consideration in the ISO for an international standard for regulatory adverse event reporting for human pharmaceuticals.

In addition to the previously described HL7-related activities, CBER is also working with CDER in the indexing of content of labeling submitted in SPL format. This activity supports the Agency goal of improving public access to information and enhances the ePrescribing initiative. Essential to the effectiveness of FDA indexing is the establishment of indexing guidance and the assessment of standard terminology using established data dictionaries. Review Management staff are leading the Center's effort to establish indexing guidelines and staff training.

Review Business Process Efforts

CBER continues to develop ways to improve the efficiency of the review business process. To achieve this goal, CBER has oversight of and works closely with the Review Management Coordinating Committee and its subcommittees to achieve consistency and harmonization of the review process across the center. The RMCC ensures that all of the Center's regulatory Standard Operating Procedures and Policies (SOPPs) are consistent with CBER's Managed Review Process. Administrative processes developed/harmonized include:

- Handling of Regulatory faxes
- Issuing Submission Numbers in Advance of the Receipt of the Electronic Submission
- Clarifying the contribution of the Office of Biostatistics and Epidemiology's to the BLA Review
- Posting and Announcement of Premarket Approval Application Approvals and Denials.

CBER's Review Management is working with its review and IT communities and the Regulatory Information Management Staff in the Office of Management to further the transition from review of paper submissions to review of electronic submissions. To more fully achieve this goal, the Center in April implemented use of a database for all pre-application submissions. These types of submissions usually involve a meeting and may lead to submission of an IND or IDE , a BLA, or a PMA or 510k. Using the new regulatory system, reviewers are able to enter information that enables the offices to coordinate communications and submissions more efficiently.

CBER works diligently with the Office of Planning in the Commissioner's Office to implement initiatives for PDUFA. These projects include IT systems management and harmonization across the centers and an Agency data standards development plan.

CBER's review community worked diligently to complete business process modeling that reflects the current state of the New Drug Application (NDA)/BLA review process. As part of this process, CBER and CDER modified their business processes to reflect appropriate harmonization for future initiatives. The modeling will be used as the basis for appropriate revisions to CBER's Managed Review Process and regulatory SOPPs.

Outreach Initiatives

CBER continues to work carefully with the Agency and the DHHS on outreach and harmonization efforts. In addition to conferences and presentations, our activities includes collaborations with the American National Standards Institute (ANSI) Health Information Technology Standards Panel (HITSP), Medications Management Workgroup, the ANSI U.S. Technical Advisory Group for ISO Technical Committee 215; Pharmacy and Health Informatics, the PhRMA Electronic Regulatory Submissions Working Group, the Electronic Adverse Reaction Reporting Working Group (eADR), the U.S. Pharmacopeia (USP) and the ICH. Review Management staff serve as the CBER lead on the ICH Steering Committee; the CBER/FDA lead for the ICH Quality Initiatives; and membership on the E2B, M5, Q10 Expert Work Groups and the Controlled Terminology Maintenance Pilot Work Group.

Review Management collaborates with OCTMA to coordinate courses designed to keep the review community informed of the latest industry standards and manufacturing processes; and continues to keep the review community informed with monthly Review Management Updates sessions. The courses include a review of the rules, guidances, and SOPPs recently published and their impact on the review community. These sessions also provide in-depth presentations on topical areas of interest to facilitate implementation of review initiatives.

CBER Review Management staff serve as the Committee Chair and Executive Secretary for the Center's Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC). This committee has representatives from offices engaged in review activity and focuses on technical and regulatory issues and consistent review processes throughout the Center. The CMCCC and its subcommittees work closely with the Agency to develop guidance documents, rule-making, and Center SOPPs to achieve harmonization and consistency with other centers on projects (e.g., Rapid Microbial Methods, Process Analytical Technologies, and the Pharmaceutical Quality Council and Subcommittees).

CBER staff also serve on several Agency standards committees and are co-chairs for CBER's Standards Management Coordinating Committee, which coordinates the Center's work with external Standards Development Organizations. The Committee, with representation from relevant offices, is tasked with strategically addressing CBER involvement in standards, and serves as a forum to discuss and develop policy and procedures for managing standards.

Document Control Center

The Document Control Center (DCC) became a part of Review Management staff in 2007 and CBER implemented several important initiatives aimed at strengthening CBER's records management program and its support of the review community:

- Upgrading the DCC Action Notice (DAN) process from a paper/email-based request format to an electronic version to facilitate reporting and feedback mechanisms for both DCC management and CBER offices.
- Developing and releasing to several product offices a pilot version of the Electronic Final Action Process (eFAP) to enable paper submissions to be filed in the DCC Product file collection, while FDA-generated correspondence is signed electronically and uploaded into the CBER Electronic Document Room. The Center plans on center-wide implementation of this program in 2008.

DCC plays an integral role in the review work of CBER by:

- Providing circulation controls for product files
- Processing incoming regulatory submissions
- Developing appropriate records management procedures for all phases of a product life cycle to ensure archiving procedures consistent with the requirements of the National Archives and Records Administration
- Working closely with the Office of Information Technology (OIT) on appropriate upgrades and modifications to the Document Tracking System (DTS), the Document Accountability and Tracking System (DATS), and the Point-to-Point (P2P) mail tracking module.
  - New hardware solutions for P2P are currently being analyzed that will replace dated technology and strengthen the mail tracking process.

DCC staff is participating in FDA Electronic Document Storage and Review (EDSR) initiative that will provide a centralized electronic content and records management capability; and secure access to all Agency electronic records, including Electronic Submissions, Correspondence, Product Reviews, and Dockets.

Global Harmonization and Outreach

The 21st century has seen the advent of a globalized environment for the life cycle of medical products, from discovery through postmarketing surveillance. Discovery, development, manufacturing, marketing, and use are all conducted in a multinational context. This new reality exists in a world where disease recognizes no national boundary. As recognized in the FDA Modernization Act, regulatory cooperation is no longer a discretionary activity. Indeed, the Act extended the FDA statutory mission to include a mandate "to participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements...."

International cooperation and efforts to harmonize standards have become important mechanisms to leverage human, scientific, and financial resources. The need for regulatory capacity building has also grown in this new global environment and represents a strategic opportunity to advance public health both domestically and abroad.

CBER responds to the demands and opportunities of this global reality through a range of interactions, some led by the Agency and others by the Center itself. The portfolio of interactions has grown significantly over the course of FY 2007, as reflected in the growing inventory summarized in this section.

World Health Organization/Pan American Health Organization Activities

CBER considers its efforts with and on behalf of the Pan American Health Organization (PAHO) and WHO to be its highest international priority. The Center continued in its second 4-year term as a designated PAHO/WHO Collaborating Center for Biological Standardization, while working with PAHO and WHO to begin the renewal process for another term. Through scientific expert consultations and laboratory collaborations, CBER staff contribute their expertise to WHO's mission to "...develop, establish, and promote international standards for biological products."

In FY 2007, CBER staff continued their participation in nearly 50 PAHO/WHO expert consultations on a variety of topics, such as potential endpoints of HIV vaccine efficacy, regulatory issues for medical devices, reviewing transgenic mouse neurovirulence test for oral polio vaccine, reviewing international biological reference preparations for Chagas diagnostic tests, drafting guidelines for clinical trials of dengue vaccines, standardizing HIV neutralization assays for use in vaccine research and clinical trials, drafting recommendations for inactivated Japanese encephalitis vaccines for human use, revising the manual for preparation and calibration of secondary reference materials, postmarketing surveillance of rotavirus vaccines, reviewing the stability of reference materials

for biological medicines and in vitro diagnostics, engaging in the PAHO network on adverse events of new vaccines, and providing the requirements for evaluation and standardization of the first international human pertussis standard. CBER also continued to provide leadership in key strategic committees and forums for WHO, including the Global Advisory Committee on Vaccine Safety, the Expert Committee on Biological Standardization (ECBS), the Immunization Strategic Advisory Group of Experts, and the Global Vaccine Research Forum.

In early 2007, WHO assessed CBER/FDA as part of that international organization's process for designating CBER a competent regulatory authority for vaccines. Any vaccine producer who wishes to have its vaccine qualify for purchase by agencies of the United Nations (e.g., UNESCO) must be prequalified by WHO. One factor in this prequalification is having oversight by a regulatory authority deemed competent by WHO.

The assessment included an on-site, two-day audit of CBER by an expert team led by WHO. Multiple components of the Center participated in this audit, including the Office of Vaccines Research and Review, the Office of Biostatistics and Epidemiology, the Office of Compliance and Biologics Quality, the Quality Assurance Staff, and the Immediate Office of the Director.

CBER continued to actively engage with the WHO Developing Country Vaccine Regulator Network (DCVRN) and the African Vaccine Regulatory Forum (AVAREF) over this period. The DCVRN is a WHO-funded network of national regulatory authorities (NRAs) from Brazil, China, Cuba, South Korea, India, Indonesia, the Russian Federation, South Africa, and Thailand. This network builds regulatory capacity among vaccine-producing developing countries through information-sharing, training, and organizing activities. Representatives from member DCVRN countries meet approximately on a biannual basis to consult with independent experts and product developers on specific issues relating to vaccine trials occurring in developing countries; and to develop institutional plans and other activities to strengthen the regulatory capacity of the developing country NRAs. CBER staff participated in the March 21–25, 2007 meeting of the DCVRN held in Brasilia, Brazil, which focused on rotavirus and dengue vaccines.

CBER staff helped organize and participated in the Second Plenary Meeting of the AVAREF held in Ouagadougou, Burkina Faso, on September 25–28, 2007. WHO coordinates this forum to assist in defining the role of NRAs of African nations in the regulation of vaccine clinical trials, in interactions with national and local Institutional Review Boards (IRBs) and ethical committees, and in strengthening the capacity of the NRAs to regulate new products.

In this capacity, FDA and other more advanced NRAs, such as the EMEA, are asked to participate as expert advisors on the regulatory mechanisms for evaluating the safety and efficacy of investigative products. The 2007 forum included representatives from 17 African nations, including Botswana, Burkina Faso, Cameroun, Ethiopia, Gabon, Gambia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, Tanzania, Uganda, and Zimbabwe, as well as expert advisors from the U.S. FDA, EMEA, and Health Canada. CBER staff made presentations on the role of FDA in foreign clinical trials and ethical oversight, as well as the responsibilities of IRBs. CBER staff also discussed clinical trial issues specific for meningococcal, HIV, malaria, and human papillomavirus (HPV) vaccines.

The ECBS recognized the need for WHO to establish a global network of regulatory authorities in the field of blood products during its 55th meeting in 2004. The ECBS recommended that WHO promote cooperation of experienced regulatory authorities and unanimously agreed that a "peer regulators group" should be established on a priority basis by experienced regulators. WHO Blood Regulators Network (BRN) was thus established in the fall of 2006 and is composed of the leading international regulatory authorities who have responsibility for the regulation of blood, blood products, and related in vitro diagnostic devices (IVDs). CBER was instrumental in the creation of the BRN and is one of its founding members. The BRN now provides its members a forum for the exchange of information and opinion on blood-related issues.

In particular, the Network focuses on scientific assessment of current and emerging threats to the safety and availability of blood and blood products, assessment of the impact of new blood-related technologies, and explores opportunities for regulatory cooperation and collaboration.

In 2007 BRN produced a "white paper" on donor selection in case of pandemic situations and a critical review of a draft WHO guideline on production, control and regulation of antivenoms. The BRN has also agreed to undertake development of criteria for assessment of national blood regulatory programs as a project in 2008.

On January 29th and 30th 2007, CBER hosted a meeting with other WHO Collaborating Centers, namely the National Institute of Biological Standards and Control (NIBSC) in the U.K., the Paul-Ehrlich-Institut (PEI) in Germany, and WHO Collaborating Center for Quality Control of Serology in Blood Banks (Sao Paulo, Brazil). The goal was to foster cooperation among the Centers and strengthen the development of WHO International Biological Reference Preparations for the control of IVD tests related to blood safety. This meeting was considered essential to support the establishment of WHO reference preparations in the IVD field through discussion on scientific issues related to IVD testing and to the major priorities and prospects of interest for each of the Centers.

In conjunction with the Scientific and Standardization Committee of the 53rd Meeting of the International Society on Thrombosis and Haemostasis (SSC-ISTH), CBER staff participated in a meeting of the WHO-ISTH Liaison Group in Geneva, Switzerland. This oversight group sets priorities for both SSC subcommittees and the coagulation reference standards to be developed and submitted to WHO for consideration by WHO ECBS. The Liaison Group recommended development of physical reference standards for Antithrombin III concentrate, Protein C concentrate, and the 6th international standard for Factor VIII/von Willbrand Factor in plasma.

In FY 2007, CBER/FDA also partnered with PAHO and the CDC to conduct a multinational active surveillance study in Brazil, Mexico, and other countries in the region that assessed rotavirus vaccine and intussusception using a self-control case series methodology. CBER staff participated in discussions led by WHO aimed at designing an efficient, multinational postlicensure surveillance system of vaccine adverse events in which countries with different healthcare infrastructure could participate. Furthermore, CBER staff have been active in a joint vaccine working group of WHO and the Council for International Organizations of Medical Sciences (CIOMS; an international, nongovernmental, nonprofit organization established jointly by WHO and UNESCO) to review, revise, and approve Brighton Collaboration vaccine adverse event definitions.

Global Collaboration for Blood Safety

WHO created the Global Collaboration for Blood Safety (GCBS) in 2000 to implement World Health Assembly Resolution 48.27 (1995) commitment to international collaboration for blood transfusion safety. This new collaboration, for which WHO provides the secretariat, is "a voluntary partnership of internationally recognized organizations, institutions, associations, agencies, and experts from developing and developed countries sharing the expertise, identifying problems, seeking solutions, and working toward the common goal of global blood safety as equal collaborative partners." This forum and partnership network facilitates international collaboration in blood safety and availability through dialogue, nonbinding recommendations, and cooperative work. CBER has played a leadership role in the GCBS since its founding.

CBER chaired the 7th General Meeting of the GCBS in Cairo, Egypt, on November 14–17, 2006, which was attended by 54 participants from 28 countries. The meeting program comprised progress reports on the activities of participating members and in-depth discussions on optimization of the transfusion chain, including selection of safe donors, providing required products to meet patient needs, and initiating transfusion practices at the bedside. The GCBS members also reviewed the structure and goals of organization as a WHO-hosted network. The next Plenary Meeting of the GCBS convened in Geneva, Switzerland, late in 2007.

Health and Consumer Protection Directorate General of the European Commission

CBER and the Health Measures Unit/Public Health and Risk Assessment (C6) of the Health and Consumer Protection Directorate General (DG SANCO) of the European Commission held an inaugural videoconference on June 6, 2007 to discuss their respective oversight frameworks for blood/blood components and cell and tissue products. Both organizations considered this a first step toward increased dialogue and communication on topics of shared interest. Shortly after the teleconference, CBER hosted a face-to-face meeting with a DG SANCO staff member.

European Union Standards and Training in the Inspection of Tissue Establishments

In 2007, CBER initiated with DG SANCO a project called EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments), whose primary objective is to optimize and harmonize the standards and methods applied by the European Union (EU) Member State Competent Authorities in the inspection and accreditation of tissue procurement and tissue establishments within the EU. The secondary objective is to propose common systems for definition, classification, and reporting of adverse events and reactions that are consistent with similar systems in other parts of the world. The project has four main components: (1) documenting best practice in the inspection of tissue and cell establishments; (2) developing practical guidelines for inspecting tissue and cell establishments; (3) designing and testing an EU training scheme for inspectors in the field; and (4)

establishing a pilot scheme for EU-wide adverse event reporting. CBER has been a "Peer Review" partner in this project, reviewing and commenting on documents it develops.

In addition, a workshop was held on May 20–24, 2007 to explore the advantages and disadvantages of different systems already in place. The participants, including each EU Member State with an inspection system in place, as well other invitees, including CBER, discussed both the strengths and weaknesses of their own systems.

The establishment of a pilot scheme for EU-wide adverse event reporting is the fourth component of this project, for which the Italian National Transplant Centre (CNT) and WHO serve as project leads. An EUSTITE Vigilance and Surveillance Medical Advisory Committee (V&S MAC) was formed to provide expert input to the effort; and WHO intends to "nest" the European project within a global context that benefits from the experience of FDA and CDC.

The EUSTITE V&S MAC held an initial meeting in Madrid, Spain, in March 2007, to which CBER sent a representative. The CNT hosted the 2nd meeting in conjunction with an initial Global Vigilance and Surveillance meeting on July 2–4, 2007, to which CBER also sent a representative. The objective was to facilitate effective communication and management of adverse events related to tissue and cell transplantation, and to explore existing systems for vigilance and surveillance and to identify strengths and weaknesses. Preliminary proposals for some common definitions and a classification system for adverse events and reactions in this field were discussed. Plans are now in place to hold such global consultations at least once a year during the 3 years of the EUSTITE project.

International Conference on Harmonization

The ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use is unique in that it brings together the regulatory authorities and pharmaceutical industry experts from Europe, Japan, and the U.S. to discuss scientific and technical aspects of product registration.

ICH also includes the participation of Health Canada, the European Free Trade Association (represented by SwissMedic), and WHO as official observers. In addition, CBER and CDER are members of the ICH Steering Committee, providing technical representation to the various expert groups that do the work of ICH (e.g., Expert Working Groups, Implementation Working Groups, Informal Discussion Groups, and Brainstorming Groups).

In FY 2007, meetings of the ICH Steering Committee and expert groups took place in Chicago, IL (October 23–26, 2006) and Brussels, Belgium (May 7–10, 2007). A series of subsequent teleconference calls during the year sustained the progress made by the Committee.

The ICH Steering Committee in Chicago took a significant step in announcing its intent to collaborate with accredited Standards Development Organizations (SDOs) to leverage the development of technical standards for ICH eInitiatives. This new effort has posed significant challenges to all parties involved, but the goal of a more globally efficient process for developing these standards is considered to be necessary and valuable.

A project aimed at developing a companion set of ICH guidelines on pharmaceutical quality and manufacturing topics--stimulated in part by FDA's GMPs for the 21st Century initiative (2003–2004)—came to fruition in FY 2007. The guidelines, "Pharmaceutical Quality Systems" (Q10) complement the earlier, "Pharmaceutical Development" (Q8) guidelines that describe what should be submitted to a regulatory authority in the relevant section of the Common Technical Document (ICH topic M4); and "Quality Risk Management" (Q9), which provides principles and examples of quality risk management that is relevant to all aspects of developing a medicinal product, submitting applications to a regulatory authority, and preparing for manufacturing site inspections.

Of particular relevance to CBER was the work of its experts in the Gene Therapy Discussion Group (GTDG), which finalized their Considerations Document on Inadvertant Germline Transmission, a document that addresses the risk of inadvertent germline integration during development of a gene therapy product. The group also began work on two new Considerations Documents: (1) Vector/Viral Shedding and (2) Oncolytic Viruses. The Steering Committee agreed that a workshop on Viral Shedding should be undertaken in the margins of the European Society for Gene Therapy in late 2007.

Global Harmonization Task Force

The Global Harmonization Task Force (GHTF) was conceived in 1992, as a response to the growing need for international harmonization in the regulation of medical devices. Primarily an engagement with FDA's CDRH and ORA, GHTF is also relevant to CBER's regulatory oversight of certain devices (e.g., cell

separation devices, blood collection containers, and HIV screening tests) that are used to prepare blood products or to ensure the safety of the blood supply. CBER staff collaborate with the CDRH representatives to the five GHTF expert study groups as warranted by CBER's regulatory responsibilities for certain devices.

Pharmaceutical Inspection Cooperation Scheme

One element of the Agency's "GMPs for the 21st Century" initiative was to pursue membership in the Pharmaceutical Inspection Cooperation Scheme (PIC/S). PIC/S is an international association of NRAs with inspectional and oversight responsibilities for medicinal products. The primary goals of PIC/S are to strengthen cooperation between the participating authorities, provide a framework for the exchange of necessary information and experience regarding inspection issues, coordinate mutual training of inspectors, and generally pursue harmonization of technical standards in the inspection of the manufacture of medicinal products. There was continued interaction between the Agency and PIC/S in FY 2007, that clarified our inspection system and regulatory framework; and CBER continues to contribute significantly to this effort.

The European Directorate for the Quality of Medicines and Healthcare Department of Biological Standardization

CBER has a well-established collaborative relationship with several committees under the shield of the Council of Europe (COE). This relationship drafted and revised the European Guide to the Preparation, Use, and Quality Control of Blood Components and provided input to the expert group that develops product standards and requirements that must be met for blood products marketed in Europe (Group of Experts 6B). This work has been an important part of efforts to harmonize U.S. blood and blood product regulations with those of Europe.

In 2007, the COE reorganized its responsibilities for blood-related activities. The result was a new, stand-alone steering committee (the CD-P-TS) that reports directly to the COE Committee of Ministers and operates with the support of the European Directorate for the Quality of Medicines and Healthcare (EDQM) Department of Biological Standardization. The new steering committee commissioned a working group (TS-GPUQA) that worked with CBER to continue the development of the Guide.

CBER staff also participated in the FY 2007 meeting of the EDQM Group of Experts 6B Meeting (Blood and Blood Products) to continue providing input and feedback on standards being developed by the group.

Regulatory Cooperation

FY 2007 saw the flourishing of CBER staff interactions with foreign regulatory counterparts as envisioned in the cooperation agreements entered into by the Agency in recent years. The discussions of safety signals, manufacturing concerns, interpretation of data, and findings significantly improved product safety and availability.

Pursuant to an information-sharing agreement, CBER staff also continued its ongoing, mutually beneficial discussions with EMEA in the areas of pharmacogenomics, pediatrics, pandemic influenza vaccines, and cancer therapeutics.

International Scientific Interactions

CBER continues its active involvement in a number of international scientific working forums, such as in the International Working Group on the Standardization of Genomic Amplification Techniques (SoGAT) for the Virological Safety Testing of Blood and Blood Products. In March 2007, CBER co-sponsored with the Japanese government the Tenth U.S.-Japan Cellular and Gene Therapy Conference with a focus on Nanobiotechnology. Seven speakers each from the U.S. and Japan were invited to discuss the advances in this multidisciplinary field and highlight FDA's activities in this cutting edge area of medical research.

As time and resources allow, CBER staff participate in international forums to provide outreach to both the regulatory and scientific global communities that benefit Center staff as well. CBER scientists have also established a number of international research collaborations.

Information Technology and System Enhancements

CBER IT staff provides value-added technology solutions in support of our regulatory processes. CBER is committed to using the best software practices and optimizing its resources to increase and maintain system functionality based on program priorities. The strong relationship between the business process group and staff continues to grow.

CBER collaborates with business and IT groups to ensure the Center's technology continues to enhance and support changes made to business processes. We look forward to making further process improvements and working together to make more effective use of IT on behalf of the regulatory processes.

In FY 2007, CBER consolidated its IT systems support from five contracts to a competitively awarded single

contract. This consolidation will allow CBER to more efficiently use resources for CBER program changes to support the development of Bioinformatics Board (BiB) and associated Business Review Board (BRB) activities.

Working closely with OITSS to provide assistance to CBER customers, the Center resolved more than 300 Employee Resource & Information Center (ERIC) trouble calls this year. CBER continues its support for CDER employees who use CBER systems, processing more than 115 account requests to access CBER regulatory applications systems in FY 2007.

A significant accomplishment was the coordinated migration of CBER's databases from Oracle 9i to Oracle 10g. This is the first of several technology refresh projects that provides better reliability and supportability in compliance with Agency standards. Next year, CBER will move the database from a VMS server platform to UNIX, and IT applications will start to be upgraded to Oracle Forms and Reports version 10g.

eSystems

CBER maintains and enhances several systems that support industry in submitting information electronically for the following three FDA forms:

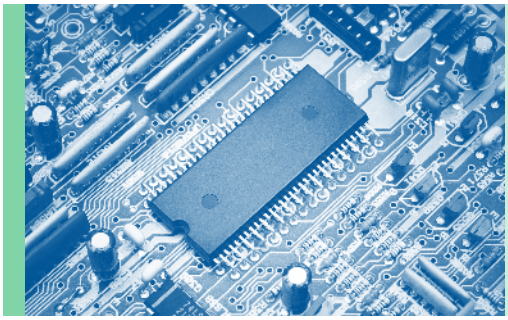
- Form FDA 2830 for Blood Establishment Registration and Product Listing
- Form FDA 3356 for Establishment Registration and Listing for Human Cells, Tissues, and Cellular- and Tissue-Based Products (HCT/Ps)
- Form FDA 3486 for Biological Product Deviation Reports (BPDRs).

Form Number	% Electronic in FY 2006	% Electronic in FY 2007
Form FDA 2830	78%	82%
Form FDA 3356	49%	69%
Form FDA 3486	74%	93%

There has been a continued increase in the number of facilities using the registration models and the total number of BPDRs entered online this year. This system sends the information directly to the appropriate Center coordinators; and because it is already in an electronic format, it makes most efficient use of CBER time and resources.

Additionally, CBER enhanced the Biologics Compliance Information System (BCIS) to improve the ability of the OCBQ to transfer potential recalls electronically into ORA's MARCS Recall Enterprise System (RES); and to retrieve classified recalls back into the BCIS Recall Tracking System (RTS) module for reporting purposes.

CBER continues to maintain query systems for use by the general public, FDA staff, and other government agencies searching registrations on blood, human cells, tissues, and cellular- and tissue-based products (HCT/ Ps). These systems reduce the number of calls to Center's Registration Coordinators, thus allowing them to focus their efforts on processing and analysis of received information.



Electronic Document Room and Electronic Submissions Gateway

CBER's Electronic Document Room (EDR) works like an electronic library for reviewers by storing electronic submissions of IND, BLA, NDA, 510(k), premarket approval (PMA), regulatory correspondence, and other CBER data. The EDR is also integrated with the CBER regulatory databases to allow advanced searches. In FY 2007, more than 2,200 electronic submissions, including BLAs, INDs, amendments, reports, and correspondence were accepted, stored, and made available to the Center review community.

One of the major EDR enhancements during 2007, was the Gateway Interface Application (GIA), which automatically validates and loads electronic submissions received from FDA Electronic Submissions Gateway (ESG). This application enables CBER to store electronic lot release protocols and regulatory communications relating to 510(k), NDA, abbreviated NDA and PMA submissions, and to consolidate the Blood Logging and Tracking document storage system into a single architecture with the CBER EDR.

FDA ESG is the central transmission point for sending information electronically to FDA, automatically routing submissions to the proper FDA Center or Office. CBER provided the Project Manager and the Lead Technical Representative for this Agency project that satisfied a PDUFA III IT Goal. In 2007, CBER received 1,149 electronic submissions via the ESG.

Biologics Investigational and Related Applications Management System

The Biologics Investigational and Related Applications Management System (BIRAMS) supports high-level tracking and summarization of CBER regulatory efforts associated with INDs, master files (MFs), IDEs, and EUAs. The system supports CBER Review Management by maintaining information on the receipt, content, and status of investigational-related application submissions, as well as FDA-generated communications, and electronic routing and review.

In FY 2007, major BIRAMS modifications included enhanced support for the CBER Electronic Review Process to reduce paper handling and expedite the routing process by means of:

- Automatic importing to EDR of signed Review documents with the attached eReview Memo
- Incorporation of the CBER electronic signature roll out
- Redesign of the Communication modules that can be reused by other CBER applications
- Creation of pre-assigned application tracking numbers for electronic Common Technical Document (eCTD) electronic submission
- Enabling the review offices to create Emergency INDs from industry communications.

Regulatory Management System for the Biologics Licensing Application

The Regulatory Management System (RMS) for the BLA is an automated system that helps CBER track BLAs, their review, and their associated data. CBER successfully implemented three major software upgrades to the RMS-BLA system comprising of more than 100 user- and programmer-generated change requests, 250 data change requests, several performance-related enhancements, and 10 special report requests. Among these enhancements were modifications and improvements in processing postmarketing commitments, new supplement letter templates for drafting FDA communications, and additional PDUFA IV changes to track and report on promotional material submissions. For processing electronic submissions, the system was modified to enable loading of BLA Original Applications and Supplements received via the ESG.

Lot-Distribution Database

The Lot-Distribution Database (LDD) system automates the collection of lot-distribution data as required by regulation. Modifications in FY 2007, include improvements for the handling of dosage and packaging information for National Drug Code (NDC) data, enhancements to the ability to track relationships between different kinds of lot numbers, and a new XML data file format that may be received via the ESG.

Security

IT security programs focus on management controls that ensure the confidentiality, integrity, and availability of systems. All CBER business systems were certified and accredited for operations in FY 2005, and are scheduled for recertification in FY 2008.

In support of the Federal Information Security Management Act of 2002 (FISMA), self-assessments and Privacy Impact Assessments (PIAs) for eight systems were completed this year. Furthermore, mitigation reports known as Plan of Actions and Milestones (POA&M) are developed on a quarterly basis. Business owners for Center systems continue to validate access lists of users and their associated roles on a quarterly basis to enhance CBER's account management processes.

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BLOODINFO
Includes all blood-related documents.

CBERINFO
Includes TISSUEINFO, BLOODINFO, and all other new CBER documents.

TISSUEINFO
Includes all tissue-related documents

APPENDIX A *CBER Publications*

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APPENDIX B *CBER Exhibits*

CBER Exhibit Program—FY 2007

Meeting	*Dates*
American Association of Blood Banks Miami Beach, FL	October 21–24, 2006
NBC4 Health and Fitness Expo Washington, DC	January 13–14, 2007
National Foundation for Infectious Diseases Conference on Vaccine Research Baltimore, MD	April 30–May 2, 2007
Plasma Protein Therapeutics Association Reston, VA	June 5–6, 2007
Rockville Economic Development, Inc. Postdoctorate Recruitment Conference 2007 Gaithersburg, MD	June 27, 2007
American Association of Tissue Banks Annual Meeting Boston, MA	September 15–18, 2007
Parenteral Drug Association/FDA Joint Regulatory Conference Washington, DC	September 24–28, 2007
International Society of Cellular Therapy 7th Annual Somatic Cell Therapy Symposium Bethesda, MD	September 26–28, 2007

APPENDIX C *CBER Major Approvals*

Biologics License Applications

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
Afluria Influenza Virus Vaccine	For active immunization to prevent influenza disease caused by influenza virus subtypes A and type B, in adults 18 years and older.	CSL Ltd ACN 45 Poplar Road Parkville, Victoria, Australia 3052
ALBAclone Anti-A (LA2) Blood grouping reagent, Anti-A (Murine Monoclonal)	Licensure of Anti-A (Murine Monoclonal) from the cell line LA2.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-B (LB3) Blood grouping reagent, Anti-B (Murine Monoclonal)	Licensure of Anti-B (Murine Monclonal) from cell line LB3.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-A,B (LA2/LB3/ES15) Blood grouping reagent, Anti-A,B (Murine Monoclonal)	Licensure of Anti-A,B (Murine Monoclonal) from the cell lines LA2, LB3, ES15.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-D Alpha (LDM1) (LDM3) Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Licensure of Blood Grouping Reagents Anti-D (Monoclonal) (IgM) from the cell line LDM1 and from the cell line LDM3.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-E (DEM1) Blood grouping reagent, Anti-E (Monoclonal)	Licensure of Anti-E (Human/Murine Monoclonal) from the cell line DEM1.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-c (H48) Blood grouping reagent, Anti-c (Monoclonal)	Licensure of Anti-c (Human/Murine Monoclonal) from the cell line H48.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-k (cellano) (LKL1) Blood grouping reagent, Anti-k (Murine Monoclonal)	Licensure of Anti-k (cellano) (Murine Monoclonal) from the cell line LKL1.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-M (LM1) Blood grouping reagent, Anti-M (Murine Monoclonal)	Licensure of Anti-M (Murine Monoclonal) from the cell line LM1.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-N (LN3) Blood grouping reagent, Anti-N (Murine Monoclonal)	Licensure of Anti-N (Murine Monoclonal) from the cell line LN3.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-Lea (LEA2) Blood grouping reagent, Anti-Lea (Murine Monoclonal)	Licensure of Anti-Lea (Murine Monoclonal) from the cell line LEA2.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703

Biologics License Applications (Continued)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
ALBAclone Anti-Leb (LEB2) Blood grouping reagent, Anti-Leb (Murine Monoclonal)	Licensure of Anti-Leb (Murine Monoclonal) from the cell line LEB2.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-Lub (LU2) Blood grouping reagent, Anti-Lub (Murine Monoclonal)	Licensure of Anti-Lub (Murine Monoclonal) from the cell line LU2.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-D Optimun (LDM1/ESD1-M) Blood grouping reagent, Anti-D (Monoclonal) (IgM Blend)	Licensure of Anti-D (Monoclonal) (IgM Blend) from the cell lines LDM1/ESD1-M.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ALBAclone Anti-D Blend (LDM3/ESD1) Blood grouping reagent, Anti-D (Monoclonal Blend)	Licensure of Anti-D (Monoclonal Blend) from the cell lines LDM3/ESD1.	Alba Bioscience, Inc. 801 Capitola Drive, Suite 9 Durham, NC 27703
ACAM2000 Smallpox (Vaccinia) Vaccine, Live	Active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.	Acambis Inc. 38 Sidney Street Cambridge, MA 02139
cobas TaqScreen West Nile Virus Test for use with the cobas s 201 system West Nile Virus/Nucleic Acid, Pooled Testing/Synthetic [cobas TaqScreen West Nile Virus Test]	For the qualitative detection of West Nile Virus (WNV) RNA in plasma specimens from individual human donors, donors of whole blood and blood components, and other living donors. It is also intended for use in testing plasma specimens to screen organ donors when specimens are obtained while the donor's heart is still beating.	Roche Molecular Systems, Inc. 4300 Hacienda Drive P.O. Box 9002 Pleasanton, CA 94566-0990
Evithrom Thrombin, Topical (Human)	An aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules are accessible and control of bleeding by standard surgical techniques is ineffective or impractical.	OMRIX Biopharmaceuticals, Ltd. 200 Chaussee De Waterloo 1640 Rhode-St-Genese, Belgium
Privigen Immune Globulin Intravenous (Human), 10% Liquid	For treatment of Primary Immunodeficiency and treatment of chronic Immune Thrombocytopenic Purpura.	CSL Behring AG 1020 First Avenue King of Prussia, PA 19406-0901
ABBOTT PRISM HCV Hepatitis C Virus Encoded Antigens (Recombinant c100-3, HCr43, NS5)	For the qualitative detection of antibodies to hepatitis C virus (anti-HCV) in human serum and plasma specimens.	Abbott Laboratories D-49C, AP6C/2 100 Abbott Park Road Chicago, IL 60064
Influenza Virus Vaccine, H5N1	For active immunization of persons ages 18–64 at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine.	Sanofi Pasteur Inc. Discovery Drive Swiftwater, PA 18370

Biologics License Applications (Continued)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
HepaGam B Hepatitis B Immune Globulin Intravenous (Human)	For the prevention of Hepatitis B recurrence following liver transplantation in HBsAg-positive liver transplant patients. Also indicated for the treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons, and household exposure to persons with acute HBV infection.	Cangene Corporation 155 Innovation Drive Winnipeg, Manitoba, Canada
CEPROTIN Protein C Concentrate (Human)	For patients with Severe Congenital Protein C Deficiency for the prevention and treatment of venous thrombosis and purpura fulminans.	Baxter Healthcare Corporation One Baxter Way Westlake Village, CA 91362
Hepatitis C Virus (HCV) Reverse Transcription (RT) Polymerase Chain Reaction (PCR) assay	Detection of Hepatitis C Virus RNA in Human Source Plasma samples by PCR.	BioLife Plasma Services, L.P. One Baxter Parkway DF3-1E Deerfield, IL 60015
Human Immunodeficiency Virus, Type 1 (HIV-1) Reverse Transcription (RT) Polymerase Chain Reaction (PCR) assay	Detection of Human Immunodeficiency Virus RNA in Human Source Plasma samples by PCR.	ioLife Plasma Services L.P. One Baxter Parkway DF3-1E Deerfield, IL 60015
ORTHO T. cruzi ELISA Test System Trypanosoma cruzi (T. cruzi) Whole Cell Lysate Antigen	Donor screening test to detect antibodies to T. cruzi in plasma and serum samples from individual human donors, including donors of whole blood, blood components or source plasma, and other living donors. It is also intended for use to screen organ and tissue donors when specimens are obtained while the donor's heart is still beating.	Ortho-Clinical Diagnostics, Inc. 1001 U.S. Highway 202 Raritan, NJ 08869-0606
Albumin (Human)	Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate.	Octapharma Pharmazeutika Produktionsgesm.b.H Oberlaaer Strasse 235 A-1100 Vienna, Austria
FluLaval Influenza Virus Vaccine	Active immunization of adults age 18 and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.	ID Biomedical Corporation of Maryland 6996 Columbia Gateway Drive, Suite 103 Columbia, MD 21046-3303

Biologics License Applications (Continued)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
Procleix Ultrio Nucleic Acid Test (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) RNA and Hepatitis C Virus (HCV) RNA	Qualitative in vitro nucleic acid assay system to screen for human immunodeficiency virus type 1 (HIV-1) RNA and hepatitis C virus (HCV) RNA in plasma and serum specimens from individual human donors, including donors of whole blood and blood components, source plasma, and other living donors. It is also intended for use in testing plasma and serum specimens to screen organ donors when specimens are obtained while the donor's heart is still beating and in testing blood specimens from cadaveric (non-heart-beating) donors.	Gen-Probe, Inc. 10210 Genetic Center Drive San Diego, CA 92121

Biologics License Supplements

(for New Indications, New Routes of Administration, New Dosage Forms, Improved Safety)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
RotaTeq Rotavirus Vaccine, Live, Oral, Pentavalent	Revised package insert: For the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4 when administered as a 3-dose series to infants between the ages of 6 to 32 weeks.	Merck & Co., Inc. P.O. Box 4 Sumneytown Pike West Point, PA 19486
FluMist Influenza Virus Vaccine Live, Intranasal	Indication Revision: For the active immunization of individuals age 2–49 against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.	MedImmune Vaccines, Inc. (a wholly owned subsidiary of MedImmune, Inc.) 297 North Bernardo Avenue Mountain View, CA 94043
FluMist Influenza Virus Vaccine Live, Intranasal	New Formulation: 2007–2008 United States formulation.	MedImmune Vaccines, Inc. 297 North Bernardo Avenue Mountain View, CA 94043
FluLaval Influenza Virus Vaccine	New Formulation: 2007–2008 United States formulation.	ID Biomedical Corporation of Quebec 525 Cartier Boulevard, West Laval, Quebec, Canada 87V 3S8
Fluvirin Influenza Virus Vaccine	New Formulation: 2007–2008 United States formulation.	Novartis Vaccines and Diagnostics Limited Gaskill Road Speke, Liverpool, L24 9GR United Kingdom
Fluarix Influenza Virus Vaccine	New Formulation: 2007–2008 United States formulation.	GlaxoSmithKline Biologicals Rue de l'Institut 89 B1330 Rixensart, Belgium

Biologics License Supplements (Continued)

(for New Indications, New Routes of Administration, New Dosage Forms, Improved Safety)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
Fluzone Influenza Virus Vaccine	New Formulation: 2007–2008 United States formulation.	Sanofi Pasteur, Inc. Discovery Drive Swiftwater, PA 18370
Zostavax Zoster Vaccine Live	Revised Package Insert: To include a statement in the package insert regarding concomitant administration of ZOSTAVAX with inactivated influenza vaccine.	Merck & Co., Inc. P.O. Box 4 Sumneytown Pike West Point, PA 19486
Carticel Autologous Cultured Chondrocytes	Revised Package Insert: To include safety and efficacy data from the Study of the Treatment of Articular Repair; and formatting and content changes in compliance with the Physician's Labeling Rule.	Genzyme Biosurgery 55 Cambridge Parkway Cambridge, MA 02142
EVICEL Fibrin Sealant (Human)	Expanded Indication: An adjunct to hemostasis for use in patients undergoing liver or vascular surgery when control of bleeding by standard surgical techniques is ineffective or impractical.	OMRIX Biopharmaceuticals, Ltd. 200 Chaussee De Waterloo 1640 Rhode-St-Genese, Belgium
Humate-P Antihemophilic Factor/von Willebrand Factor Complex (Human)	Additional Indication: For adult and pediatric patients with von Willebrand disease for the prevention of excessive bleeding pre- and postsurgery.	CSL Behring GmbH 1020 First Avenue King of Prussia, PA 19406
TWINRIX xxx Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine	Revised Package Insert: For an accelerated dosing schedule of 0, 7, 21–30 days, and a month 12 booster dose.	GlaxoSmithKline Biologicals Rue de l'Institut 89 B1330 Rixensart, Belgium
Rhophylac Rho(D) Immune Globulin Intravenous (Human)	Expanded indication: for the treatment of Rho(D) positive, non-splenectomized adult patients with chronic Immune Thrombocytopenia Purpura (ITP).	ZLB Behring AG 1020 First Avenue King of Prussia, PA 19406-0901
Alphanate Antihemophilic Factor (Human)	Additional Indication: For surgical and/ or invasive procedures in patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.	Grifols Biologicals, Inc. 5555 Valley Boulevard Los Angeles, CA 90032
Engerix-B Hepatitis B Vaccine (Recombinant)	New Formulation: Thimerosal-free formulation.	GlaxoSmithKline Biologicals Rue de l'Institut 89 B1330 Rixensart, Belgium

Biologics License Supplements (Continued)

(for New Indications, New Routes of Administration, New Dosage Forms, Improved Safety)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
FluMist Influenza Virus Vaccine Live, Intranasal	New Formulation: Convert from the frozen formulation to a liquid formulation.	MedImmune Vaccines, Inc. (a wholly owned subsidiary of MedImmune, Inc.) 297 North Bernardo Avenue Mountain View, CA 94043
Flebogamma 5% DIF Immune Globulin Intravenous (Human)	New Formulation: Addition of a viral inactivation step, new manufacturing facility, and a 400-mL fill size.	Instituto Grifols, S.A. 2 Can Guasch St Poligono Levante Parets del Valles Barcelona, Spain 0815
NovoSeven Coagulation Factor VIIa (Recombinant)	Additional Indication: Treatment of bleeding episodes and for the prevention of bleeding in surgical interventions or invasive procedures in patients with acquired hemophilia.	Novo Nordisk A/S Novo Nordisk Pharmaceuticals, Inc. 100 College Road West Princeton, NJ 08540

Device Applications

Tradename	Description and Indication for Device	Applicant
CryoSeal FS System	For use in the automated preparation of fibrin sealant from a single unit of autologous human plasma only in a closed, sterile fluid path. The autologous fibrin sealant prepared by this device is indicated for use as an adjunct to hemostasis on the incised liver surface in patients undergoing liver resection when control of bleeding by standard surgical techniques is ineffective or impractical.	ThermoGenesis Corporation 2711 Citrus Road Rancho Cordova, CA 95742
COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, 48 Tests/COBAS AmpliPrep/COBAS TaqMan Wash Reagent, 5.1 L	This test is an in vitro nucleic acid amplification test for the quantitation of Human Immunodeficiency Virus Type I (HIV-1) RNA in human plasma.	Roche Molecular System, Inc. 4300 Hacienda Drive Pleasanton, CA 94566
Abbott RealTime HIV-1 Amplification Reagent Kit, Abbott RealTime HIV-1 Calibrator Kit, Abbott RealTime HIV-1 Control Kit	Quantitation of Human Immunodeficiency Virus type 1 (HIV-1) on the automated m2000 System in human plasma for use in conjunction with clinical presentation and other laboratory markers.	ABBOTT Molecular, Inc. Des Plaines, IL

APPENDIX D *Rulemaking and Guidance Documents*

Rulemaking and Guidance Documents for FY2007

Rulemakings

A. The following proposed and final rules and final orders were issued by CBER and published in the Federal Register in FY 2007:

- Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Direct Final Rule—8/15/2007
- Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Companion Document to Direct Final Rule; Proposed Rule—8/15/2007
- Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection ("Lookback"); Final Rule—8/24/2007
- Medical Devices: Immunology and Microbiology Devices: Classification of In Vitro Human Immunodeficiency Virus Drug Resistance Genotype Assay; Final Rule—8/8/2007
- Human Cells, Tissues, and Cellular- and Tissue-Based Products; Donor Screening and Testing, and Related Labeling; Final Rule—6/19/2007
- Blood Vessels Recovered with Organs and Intended for Use in Organ Transplantation; Final Rule—3/12/2007
- Medical Devices; Hematology and Pathology Devices; Classification of Cord Blood Processing System and Storage Container; Final Rule—1/31/2007
- Distribution of Blood Derivatives by Registered Blood Establishments that Qualify as Healthcare Entities; Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Delay of Applicability Date; Final Rule; Delay of Applicability Date—11/13/2006

B. CBER/Policy Staff was involved in the clearance of the following published proposed and final rules for which other FDA Centers/Offices were the lead:

- Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants; Proposed Rule—1/12/2007
- Medical Device Regulations; Disqualification of a Clinical Investigator; Final Rule; Technical Amendment—12/22/2006
- Expanded Access to Investigational Drugs for Treatment Use; Proposed Rule—12/13/2006
- Charging for Investigational Drugs; Proposed Rule—12/13/2006

Guidance Documents

(Guidance documents can be viewed at http://www.fda.gov/cber/guidelines.htm)

A. The following guidance documents were issued by CBER and posted and/or published in FY 2007:

- Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials—9/27/2007
- Guidance for Industry: Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms—9/6/2007
- Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular- and Tissue-Based Products (HCT/Ps)—Small Entity Compliance Guide—8/24/2007

- Guidance for Industry: "Lookback" for Hepatitis C Virus (HCV):Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV—8/24/2007
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular- and Tissue-Based Products (HCT/Ps)—8/8/2007
- Guidance for Industry: Class II Special Controls Guidance Document: In Vitro HIV Drug Resistance Genotype Assay—8/8/2007
- Guidance for Industry: Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes—8/7/2007
- Draft Guidance for Industry: Cell Selection Devices for Point-of-Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs)—7/23/2007
- Draft Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics—7/20/2007
- Draft Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage—7/6/2007
- Guidance for Industry: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs—6/20/2007
- Draft Guidance for Industry: "Computer Crossmatch" (Electronic-Based Testing for the Compatibility between the Donor's Cell Type and the Recipient's Serum or Plasma Type)—6/20/2007
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines—5/31/2007
- Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines—5/31/2007
- Guidance for Industry: Class II Special Controls Guidance Document: Cord Blood Processing System and Storage Container—1/31/2007
- Guidance for Industry: Certain Human Cells, Tissues, and Cellular- and Tissue-Based Products (HCT/Ps) Recovered from Donors Who Were Tested for Communicable Diseases Using Pooled Specimens or Diagnostic Tests—1/23/2007
- Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies—1/16/2007
- International Conference on Harmonisation (ICH); Draft Guidance: E15 Terminology in Pharmacogenomics—1/8/2007
- Guidance for Industry: Gene Therapy Clinical Trials—Observing Subjects for Delayed Adverse Events—11/28/2006
- Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors—11/28/2006
- Guidance for Industry: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components—10/27/2006
- Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components—10/18/2006
- Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments—10/18/2006

B. CBER/Policy Staff was involved in the clearance of the following published draft and final guidances for which other FDA Centers/Offices were the lead:

- Guidance for Industry and FDA Staff: Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions—9/13/2007
- Draft Guidance for Industry: Pharmacogenomic Data Submissions—Companion Guidance - 8/28/2007
- Guidance: Emergency Use Authorization of Medical Products—7/31/2007
- Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996—7/24/2007
- Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays—7/24/2007
- International Conference on Harmonisation (ICH); Draft Guidance: Q10 Pharmaceutical Quality System—7/12/2007
- Draft Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document—7/2/2007
- Guidance for Industry and FDA Staff: Bundling Multiple Devices or Multiple Indications in a Single Submission—6/22/2007
- Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Receipt Date—6/5/2007
- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics—5/15/2007
- Guidance for Industry: Computerized Systems Used in Clinical Investigations—5/10/2007
- Draft Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects—Supervisory Responsibilities of Investigators—5/10/2007
- Draft Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting—Improving Human Subject Protection—4/17/2007
- Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products—Content and Format—4/9/2007
- Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees—3/2007
- Draft Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process—3/26/2007
- Draft Guidance for Industry: Advisory Committee Meetings—Preparation and Public Availability of Information Given to Advisory Committee Members—2/27/2007
- Draft Guidance for Industry: Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration—2/27/2007
- Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA Under 21 CFR 50.54—Additional Safeguards for Children in Clinical Investigations—12/22/2006
- Draft Guidance for Industry and FDA Staff—Annual Reports for Approved Premarket Approval Applications (PMA)—10/26/2006
- Guidance for Industry: Bar Code Label Requirements—Questions and Answers—10/5/2006

APPENDIX E *Advisory Committee Meetings*

Blood Products Advisory Committee

- December 14, 2006
  - *Committee Updates*
    Summary of the October 11, 2006 Public Hearing on Emergency Research
  - *Open Discussion Topics*
    Preclinical and clinical studies on the hemoglobin-based oxygen carrier, bovine polymerized hemoglobin (HBOC-201).

- April 26–27, 2007
  - *Committee Updates*
    Summary of August 30–31, 2006, meeting of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability; Summary of December 15, 2006, meeting of the Transmissible Spongiform Encephalopathies Advisory Committee on FDA's risk communication on plasma-derived Factor VIII and Factor XI; Summary of September 25–26, 2006, FDA Workshop on Molecular Methods in Immunohematology.
  - *Open Discussion Topics*
    Issues related to implementation of blood donor screening for infection with Trypanosoma cruzi and issues related to transmissibility of Trypanosoma cruzi in donors of human cells, tissue, and cellular- and tissue-based products; Transfusion-related acute lung injury; Issues related to implementation of blood donor screening for infection with West Nile Virus

- August 16, 2007
  - *Committee Updates*
    Summary of the May 10–11, 2007, and the August 6–7, 2007, meetings of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability; Summary of the April 25–26, 2007, FDA Workshop on Immune Globulins for Primary Immune Deficiency Diseases: Antibody Specificity, Potency, and Testing; Summary of the August 15, 2007, FDA Workshop on Licensure of Apheresis Blood Products.
  - *Informational Presentations*
    World Health Organization (WHO) biological standards on the following topics: Summary of the January 29–30, 2007, WHO meeting with WHO collaborating centers for biological standards and standardization to support the development of WHO biological reference preparations for high-risk blood safety-related in vitro diagnostics; Potency and safety standards for plasma derivatives; and Joint FDA/WHO minimum potency standards for certain blood grouping reagents.
  - *Open Discussion Topics*
    Response of the Office of Blood Research and Review to their office level site visit of July 22, 2005; Measles antibody levels in U.S. Immune Globulin products.

Cellular, Tissue and Gene Therapies Advisory Committee

- November 20, 2006
  - *Open Discussion Topics*
    Research programs in the Laboratory of Immunobiology and the Laboratory of Immunology, Office of Biotechnology Products, Center for Drug Evaluation and Research.
  - Closed Discussion Topics: Individual FDA research programs.

- March 29–30, 2007
  - *Open Discussion Topics*
    Sipuleucel-T, Dendreon (BLA-STN 125197) indicated for the treatment of men with asymptomatic metastatic hormone refractory prostate cancer; Draft document entitled "Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies"; Overviews of research programs in the Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research.
  - *Closed Discussion Topics:* Individual FDA research programs.

- July 26, 2007
  - *Open Discussion Topics*
    Research programs in: (1) The Division of Therapeutic Proteins and the Division of Monoclonal Antibodies, Office of Biotechnology Products, Center for Drug Evaluation and Research, FDA; and (2) The Division of Cellular and Gene Therapies, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research, FDA.
  - *Closed Discussion Topics:* Individual FDA research programs

Transmissible Spongiform Encephalopathies Advisory Committee

- December 15, 2006
  - Open Discussion Topics: FDA's risk assessment for potential exposure to variant Creutzfeldt-Jakob disease in human plasma-derived antihemophilic factor (FVIII) products manufactured from U.S. plasma donors and related communication materials; Levels of transmissible spongiform encephalopathy clearance in the manufacture of plasma-derived Factor VIII products.

Vaccines and Related Biological Products

- November 16, 2006
  - *Open Discussion Topics*
    The Laboratory of Bacterial Toxins, Division of Bacterial, Parasitic, and Allergenic Products; and the Laboratory of Vector-Borne Virus Diseases, the Laboratory of Hepatitis Viruses, and the Laboratory of Respiratory Viral Diseases, Division of Viral Products, Office of Vaccines Research and Review, CBER.
  - *Closed Discussion Topics:* Individual FDA research programs.

- January 25, 2007
  - *Open Discussion Topics*
    Safety and immunogenicity of Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (DTaP-IPV/Hib), PENTACEL, manufactured by Sanofi Pasteur Limited; Research programs in the Office of Vaccines Research and Review, CBER.
  - *Closed Discussion Topics:* Site Visit Report of research program.

- February 27–28, 2007
  - Open Discussion Topics
    Safety and effectiveness of an H5N1 inactivated influenza vaccine manufactured by Sanofi Pasteur Limited; Clinical development of influenza vaccines for pre-pandemic uses; Strain selections for the influenza virus vaccine for the 2007–2008 season; Circulating lineages of influenza type B virus.

- May 16–17, 2007
  - *Open Discussion Topics*
    Safety and effectiveness of influenza virus vaccine live (FluMist) in a pediatric population less than 59 months of age, manufactured by MedImmune Vaccines, Inc.; Safety and immunogenicity of a live vaccinia virus smallpox vaccine (ACAM2000) manufactured by Acambis, Inc.; Research Programs Laboratory of Bacterial Polysaccharides and the Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial Parasitic and Allergenic Products, Office of Vaccines Research and Review, CBER.
  - Closed Discussion Topics: Individual FDA research programs.
  - Committee Update: The influenza strain selection for the 2007–2008 influenza season.

APPENDIX F *CBER Workload Data*

Biologics License Applications

	FY 05	FY 06	FY 07
Investigational New Drugs and Devices			
Original INDs/IDEs	281	266	277
Master Files	51	45	47
IND/IDE/MF Amendments	8,581	9,124	10,223
Currently Active INDs/IDEs/MFs and Amendments	2,687	2,855	2,968
Premarket Submissions			
Original BLAs	25	56	23
BLA Supplements	1,675	1,716	1,742
PMAs and PMA Supplements	19	15	30
510(k)s	63	60	58
NDAs and NDA Supplements	13	63	31
ANDAs and ANDA Supplements	5	13	12
Orphan Biological Designations	1	0	3
Reports, Registrations, Reviews			
Adverse Event System Reports			
(includes VAERS, MEDWatch and Foreign Reports)	21,902	21,956	28,255
Biological Product Deviation Reports	38,757	38,618	43,345
Blood Establishment Registrations	2,654	2,626	2,610
Tissue Establishment Registrations	1,929	2,322	2,650
Advertising and Promotional Labeling Review Submissions	3,762	2,962	3,169

Key

IND = Investigational New Drug

IDE = Investigational Device Exemption

MF = Master File

BLA = Biologics License Application

NDA = New Drug Application

ANDA = Abbreviated New Drug Application

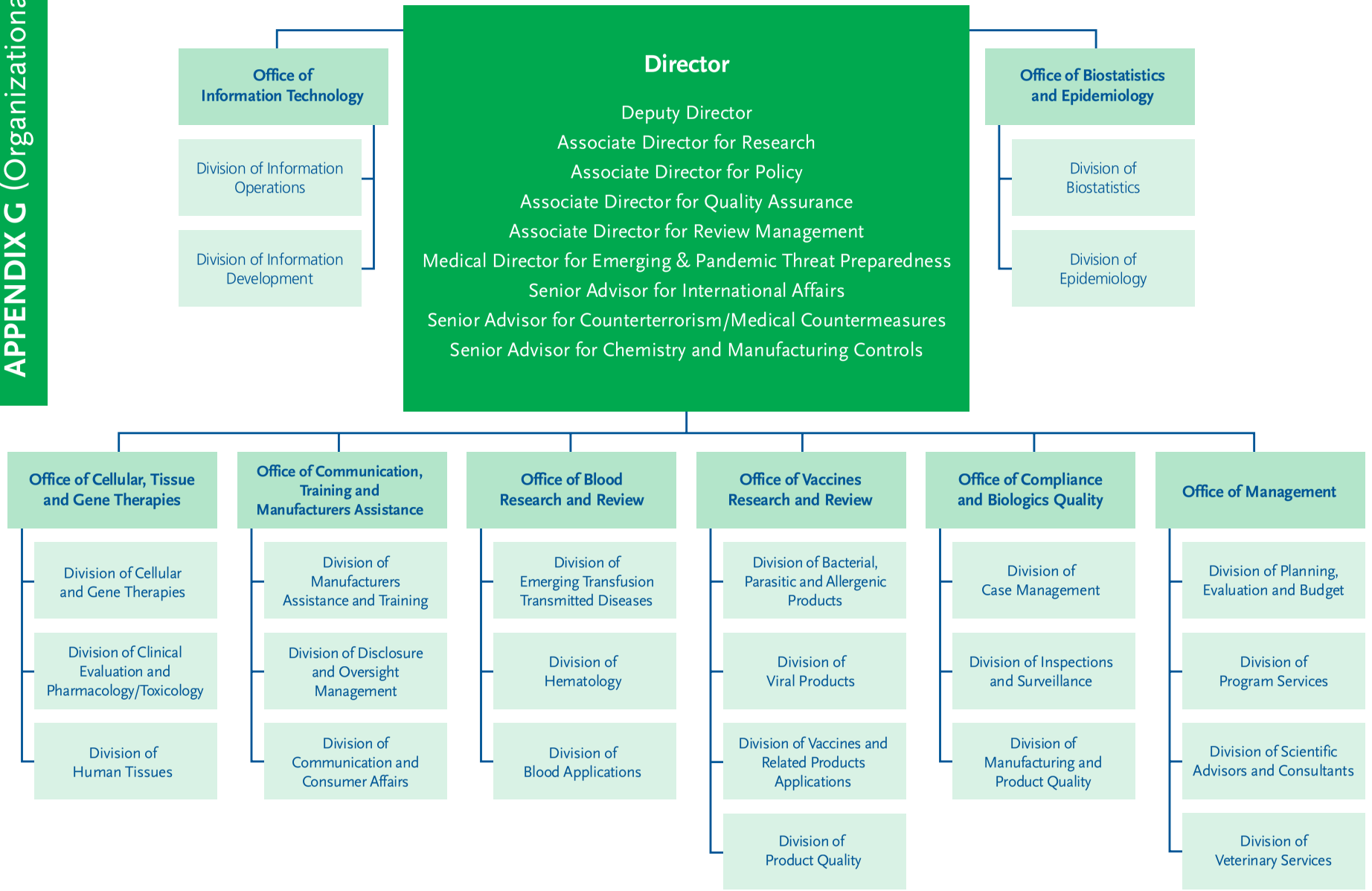
PMA = Premarket Approval Application for Class III medical devices

510(k) = Premarket submission to demonstrate that the device to be marketed is substantially equivalent to a legally marketed device that is not subject to a PMA

VAERS = Vaccine Adverse Event Reporting System

APPENDIX G (Organizational Chart)

Center For Biologics Evaluation And Research



A TRIBUTE TO DR. EDA T. BLOOM

This tribute to Dr. Eda T. Bloom recognizes her outstanding achievements and dedication to advancing public health, especially in the field of xenotransplantation. Dr. Bloom died unexpectedly in January 2008.

Dr. Bloom joined CBER in 1989, in the Division of Cytokine Biology where she performed research on natural killer (NK) cells, and applied her scientific expertise to the review and development of policy on early somatic cell therapy products. In 1991, Dr. Bloom became head of the Section of Molecular and Cell Biology. In 1992, Dr. Bloom moved to the Division of Cellular and Gene Therapies, where she was promoted to Chief of the Laboratory of Cellular Immunology, recently renamed Gene Transfer and Immunogenicity Branch. In 1996, in recognition of Dr. Bloom's outstanding research and regulatory accomplishments, she was selected for the Senior Biomedical Research Service.

Dr. Bloom's research made significant public health contributions in several areas. Her work on NK cells continued, with efforts to optimize NK cell activity through oxidation-reduction mechanisms. She initiated studies of the human anti-pig immune response, with the hope of finding ways to reduce this response and ultimately to prevent rejection of porcine xenotransplantation products in humans. Under her leadership, she and her colleagues studied the NK response against endothelial cells, target cells of direct relevance to vascularized xenotransplantation products.

The idea of trying to prevent an immune response in the xenotransplantation setting led to the study of regulatory T cells (Tregs). These cells suppress T cell responses in autoimmune, transplantation, and cancer settings. Dr. Bloom's laboratory isolated Tregs from human and baboon blood, and showed that addition of these cells to the culture could suppress anti-pig responses by human immune effector cells. In her most recent research, Dr. Bloom studied the immune response against allogeneic human embryonic stem cell-derived products.

For the past 10 years, Dr. Bloom served as the Chair of FDA's Xenotransplantation Committee. She was influential in coauthoring and implementing the PHS Guideline on Infectious Disease Issues in Xenotransplantation (http://www.fda.gov/cber/guidelines.htm) and other important regulatory documents. She planned and participated in both FDA and the DHHS Secretary's Advisory Committee meetings on a series of topics in the field of xenotransplantation. Dr. Bloom was instrumental in the review of the first and only xenotransplantation product approved to date (2007) under the Humanitarian Device Exemption for use in wound healing of severe burn victims.

Dr. Bloom received numerous awards for her regulatory contributions to the field of xenotransplantation, including the FDA Commissioner's Special Citation in 1998 and 2004. Dr. Bloom also made important contributions through her interactions with a variety of international governmental and non-governmental bodies. She served as a U.S. representative to the Council of Europe's Working Party on Xenotransplantation, and to the WHO Consultation on Xenotransplantation and related WHO consultations.

For all of her friends and colleagues, especially those in the fields of immunology and xenotransplantation, Dr. Eda Bloom served as a role model and mentor, in her quest for knowledge about xenotransplantation. Dr. Bloom's research, as well as her warmth, generosity, and leadership have left this field with a strong legacy and contribution to public health.

U.S. Department of Health and Human Services
Food and Drug Administration