Organizational Changes

In 1955, as a result of the Cutter Incident, the Laboratory of Biologics Control was raised to division status within NIH, to strengthen and expand its biologics control function. It became the Division of Biologics Standards, an independent entity composed of seven laboratories. The Division continued to oversee the control and release of biologics until 1972, when, in reaction to its not having instituted an effectiveness review equivalent to that performed for drugs, it was moved from NIH to FDA and renamed the Bureau of Biologics. The merger with FDA was logical, because a "biological product" under the 1944 PHS Act also falls within the jurisdiction of the 1938 FD&C Act. The appropriate provisions of both Acts were skillfully used to regulate biologics.

Amendments to the Food, Drug, and Cosmetic Act

Certain amendments to the 1938 FD&C Act during these years affected biologics. In 1951, the Durham-Humphrey Amendment defined the kinds of drugs that could not be used safely without medical supervision and required them to be sold "by prescription only." And, in 1962, Congress passed the Kefauver-Harris Amendments after thalidomide, a new sleeping pill used widely in Europe, was found to cause birth defects. It has been claimed that there were between 10,000 and 20,000 babies born disabled in Europe as a consequence of the drug, but numbers vary among sources. FDA had kept thalidomide from being marketed in the United States. But, as part of a pharmaceutical company's investigational trial, physicians gave the drug to more than 20,000 U.S. patients, 624 of whom were pregnant. There were 17 documented cases of American children born with defects caused by thalidomide—ten from the U.S. trial and seven from thalidomide obtained in Europe. To prevent similar calamities, the 1962 amendments strengthened the regulations for drug safety and for testing drugs in clinical trials. Also, they required manufacturers to provide "substantial evidence" that their drugs were effective for the intended use. Further, they required that drugs must be manufactured using "good manufacturing practices," required inspection of commercial manufacturers once every two years, and required annual registration of manufacturers. These amendments also applied to blood banks.

Testing Blood for Hepatitis B

Hepatitis B is a viral disease that occurs worldwide. The virus is found in body fluids of people who clearly have infections, as well as people who are carriers of the virus but show no hepatitis symptoms. Unlike hepatitis A virus, which is commonly spread by ingesting the virus in contaminated food, hepatitis B virus is transmitted mostly through injection—for example, by blood transfusion or by sharing needles among drug users. Research in the 1950s confirmed that post-transfusion hepatitis can be caused by either whole blood or plasma from virus carriers. Around 1970, methods for the detection of hepatitis B virus surface antigen (HBsAg) were developed that could be used to screen blood for the virus. Test kits for HBsAg were first licensed by the Division of Biologics Standards (DBS) in February 1971 and, in November 1971, DBS published a requirement that all blood collected under license must be tested for HBsAg. Licensing by DBS was initially required for blood banks engaged in interstate shipment of blood, but not for blood banks that operated only within state borders. On July 1, 1972, the requirement that the HBsAg test be performed on all blood collected under license became effective. As technology improved, more sensitive tests for HBsAg were developed and licensed. By December 1975, all registered blood establishments were required to use these more sensitive tests. This requirement was more comprehensive than the one that became effective in 1972, because "registered" establishments included those involved in interstate shipment of blood and those operating only within state borders. In the early 1970s, the risk of contracting some form of hepatitis from a unit of blood was as high as six to eight percent. Now, the risk of contracting hepatitis B from a pint of blood is about 1 in 200,000.

Legal Action Against Blood Banks

The first prosecution of a licensed blood bank occurred in 1962, when the Division of Biologics Standards brought suit against John Calise and the Westchester Blood Bank in New York, for altering the expiration dates on whole blood to dates that were beyond the 21-day expiration date requirement. This was the first litigation brought against a manufacturer under the Biologics Control Act of 1902. Calise pleaded guilty and, in 1964, was convicted on three counts of misbranding, three counts of false labeling, two counts of shipping an unlicensed biological product, and one count of conspiracy. He was placed on probation for five years and forbidden to take part in the manufacture, distribution, or sale of any biologics, including blood products. This case represented the first time a court had declared that blood was a drug, as defined by the FD&C Act of 1938. There were other prosecutions of blood banks in the 1960s. For instance, in 1963, an outbreak of hepatitis was linked to the commercial Paterson Blood Bank, Inc., (PBB) in Paterson, New Jersey. Investigators traced the likely sources of the contamination to tattooing and to blood sold by known narcotics addicts to a local unlicensed blood bank, that sold the blood to PBB. In July 1964, the president of PBB was found guilty of selling blood from an unlicensed bank in interstate commerce, as well as falsely labeling blood with dates past the 21-day expiration date. The PBB also was convicted of numerous charges, including mislabeling blood that was reactive for syphilis as being nonreactive.

The Challenge of Regulating Blood Products

The Laboratory of Biologics Control issued the first blood bank license and the first license for interstate shipment of blood to the Philadelphia Blood Bank in 1946. Regulating blood products posed considerable challenges for the Laboratory and, after 1955, for the Division of Biologics Standards. For example, they licensed only facilities that shipped blood between states; thus, they had no control over blood banks operating within states. Also, mislabeling blood products and altering the expiration dates (to increase profits) was easy for commercial blood banks. And, interpretation by the courts of the laws regulating blood products was not entirely consistent. For instance, in 1968, a Dallas blood bank was found guilty of mislabeling Whole Blood and Red Blood Cells shipped in interstate commerce. A Court of Appeals overturned the guilty verdict on the basis that Citrated Whole Blood (blood containing an anticoagulant) and Red Blood Cells were not products similar to a therapeutic serum and so could not be regulated under the 1944 PHS Act. Because of this decision, the terms "blood, blood components, and derivatives" were inserted into the 1944 PHS Act in October 1970.

After establishment of the Bureau of Biologics within FDA in 1972, the agency reviewed the safety, effectiveness, and labeling of all previously licensed biologics. Regulatory activity increased, especially for blood and blood products. Interstate blood banks were still licensed under the 1944 PHS Act, but all intrastate blood banks (operating only within states) were subject to the 1962 Kefauver-Harris Amendments. By 1973, the Bureau had oversight of almost 7,000 blood facilities. In addition, regulations were published in 1973 that required licensing of all establishments that collected blood plasma by plasmapheresis, that is, by harvesting the plasma and returning the cells to the donor. And new regulations in 1975 established standards (good manufacturing practices) for the operation of all blood banks. By December 1975, all registered blood establishments were required to test for hepatitis B with tests of third-generation (meaning the highest) sensitivity.

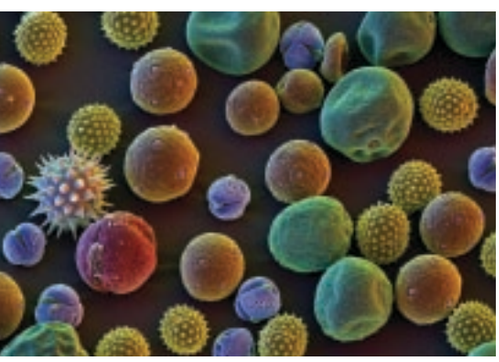
Andrew Young performs ultracentrifugation studies to detect changes that occur during the storage of blood derivatives, 1964

John S. Finlayson, PhD, CBER Office of Blood Research and Review. In the 1950s–1980s he conducted research on plasma proteins.

DNA molecule
Courtesy of National Institutes of Health

Ensuring Effectiveness of Allergenic Products

Allergenic products include allergen patch tests—diagnostic tests applied to the surface of the skin, and allergenic extracts—injectable products, made from natural substances, used to diagnose and treat allergic diseases such as "hay fever," food allergy, and bee venom allergy. Very important research on allergenic products, particularly allergenic extracts, began in the 1970s in the Bureau of Biologics. As explained by Harold Baer, former Chief of the Laboratory of Allergenic Products, "although there were hundreds of allergenic products, and many were injected into numerous people, these were the only products for which there were no standards." To address this issue, Bureau scientists developed laboratory techniques for measuring the activity of allergenic extracts, linked these results to effectiveness of the extracts in humans, and established standards for the extracts that had to be met by manufacturers. A scientific review of the hundreds of allergenic extracts that were being marketed in the United States in the 1980s found that about 240 products had no allergenic activity. These ineffective products were gradually removed from the market over the course of a decade.



Mixed pollen grains
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Noteworthy Achievements

Several events of global significance that occurred between 1951 and 1980 deserve mention. First, in 1953, James Watson (American) and Francis Crick (British) determined that the structure of DNA, the molecule that holds genetic information, is a "double helix." They also realized that this structure could make copies of itself. Because genes are made of DNA, these discoveries were the foundation for the development of biotechnology—the manipulation of genes and genetic characteristics of living things. In the early 1970s, scientists discovered how to insert foreign genes into bacteria, a huge scientific advance that set the stage for producing biologics by using "biotech" methods.

The development of hybrid cells, commonly called hybridomas, by Georges Köhler (German) and Cesar Milstein (Argentine) in 1975 was another scientific advance that had significant consequences for biologics and for modern medicine. These scientists physically fused cancerous mouse plasma cells (plasmacytoma cells) with mouse lymphocytes (cells responsible for immunity) to form the hybrid cells, which could survive indefinitely in tissue culture and produce specific antibodies. Their research laid the foundation for large-scale production of monoclonal antibodies. In this process, plasmacytoma cells are fused with spleen cells from a mouse that has been immunized against an antigen of interest. Only a few of the hybridomas (about 1 in 500) will produce antibodies to the antigen. Once a hybridoma "clone" is selected, however, it can be grown in large quantities and an unlimited amount of specific "monoclonal" antibodies can be made for the diagnosis and treatment of disease.

Arcadia, California newcomers receive vaccination against smallpox, 1942
Courtesy of National Archives and Records Administration

In addition, the global eradication of smallpox was accomplished during this period, an effort that had its beginnings in 1950 when the Pan American Sanitary Organization made a commitment to eradicate smallpox in the western hemisphere. The World Health Organization (WHO) undertook an initial global eradication program in 1959, but the results were disappointing. Then, in December 1966, encouraged by the commitment of the Centers for Disease Control (CDC) of the PHS to wipe out smallpox in Africa, WHO funded an intensified, well-organized global program to eliminate smallpox worldwide within ten years. CDC staff directed the worldwide effort and also conducted the program in Africa. The last naturally occurring case of smallpox was reported in Somalia in October 1977. In May 1980, WHO announced that worldwide elimination of the disease had been achieved. The elimination of smallpox illustrates how effective international collaboration can be in improving human health.

Roderick Murray, Division of Biologics Standards, 1955-1972

Barbara Jackson, Laboratory of Viral Immunology, worked with the Meyer-Parkman team

Protection Against Rubella

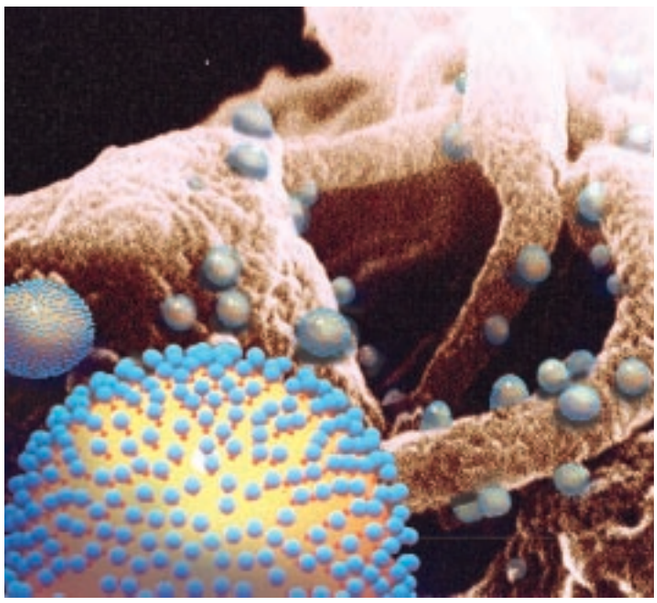
Rubella (German measles) is a usually mild viral disease that most often affects children and young adults. But, it is a very dangerous disease for pregnant women, particularly during the first three months of pregnancy. The virus can be transmitted to the unborn child, resulting in abnormalities such as cataracts, deafness, heart defects, and mental retardation. A global epidemic of rubella that started in Europe in 1962 spread to the United States in 1964, causing an estimated 12.5 million cases in this country and birth defects in about 20,000 children. The need for a rubella vaccine was clear, and many in the scientific community were working on the problem. In 1963, Roderick Murray, MD, the founding Director of the Division of Biologics Standards (DBS), hired Paul Parkman, MD, who had discovered rubella virus while working at the Walter Reed Army Institute of Research, to start a rubella program. Dr. Parkman teamed with Harry Meyer, Jr., MD, already at DBS. By 1966, they were able to report that they had developed the first effective experimental vaccine for rubella. They had weakened the rubella virus by subjecting it to 77 passages in primary African green monkey kidney cell cultures over two years and then tested its effectiveness in rhesus monkeys. When the monkeys were inoculated with the weakened, live virus, none of them developed rubella or transmitted the disease to monkeys that had not been inoculated, and they were solidly protected against infection with the wild virus. Based on these results, Parkman and Meyer prepared a weakened, live vaccine for human testing and inoculated 34 children. None of the children developed rubella; also, the children did not transmit the vaccine virus infection to any of their 30 playmates who had not been inoculated. Parkman and Meyer made the weakened virus, the first successful experimental rubella vaccine, available to other scientists interested in rubella research. Based on their success, the first rubella vaccines were licensed in 1969. These vaccines, and the current vaccine that was approved a decade later, have been strikingly successful in controlling rubella. By 1988, there were only 225 reported cases of rubella in the United States.

Paul Parkman and Harry Meyer, developers of the rubella vaccine, 1966

Discovery and Change: 1981 through 2000

During these years, scientific achievements and challenges related to biologics came fast and furiously. To keep pace with rapidly changing technology, new discoveries, and the difficulty of regulating an ever-growing number of biologic products, organizational changes transformed the Bureau of Biologics into CBER, as it exists today.

HIV virus
Courtesy of National Institutes of Health



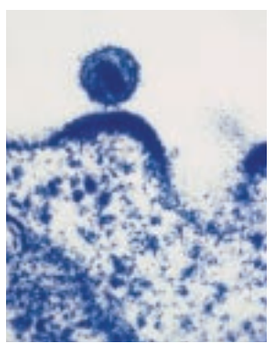
Screening Blood for HIV

The blood supply plays a vital role in the American health system, and CBER is responsible for ensuring the safety of that supply. The appearance of AIDS in the United States in 1981 threatened the safety of the U.S. blood supply, because the Human Immunodeficiency Virus (HIV) that causes AIDS is found in the blood of people with the disease, as well as in the blood of people who have been exposed to the virus but who are not yet ill. HIV was not identified as the cause of AIDS until 1984. There are two types of HIV: HIV-1, found worldwide, and HIV-2, found mostly in West Africa. Once HIV was identified and characterized, scientists were able to develop tests to detect HIV in blood. In 1985, CBER licensed the first test kit to screen donated blood for antibodies to HIV-1 (the presence of antibodies means the individual has been exposed to HIV-1) and licensed a more accurate test, the Western Blot Test, in 1987. Since the mid-1980s, screening tests for both HIV-1 and HIV-2 have been continually improved. CBER published regulations in 1987 that required HIV screening, with tests that detect HIV antibodies, of all blood and blood plasma collected in the United States. "With the advent of the screening tests for HIV, enforcement and compliance activities focused on ensuring that blood establishments were conducting the screening tests properly...," according to Steven Masiello, Director of CBER's Office of Compliance and Biologics Quality. In March 1996, the first antigen test kit for screening blood for HIV-1 was licensed. It is used in addition to HIV antibody tests. HIV antigen appears in the blood of an HIV-infected person about one week earlier than HIV antibodies, which usually appear within three months after infection. Thus, an HIV-antigen test reduces the "window" period, when blood could be HIV-infected, but still have negative antibody tests. It has been estimated that HIV-1 antigen screening prevents five to ten cases of AIDS per year. In 1985, the risk of HIV infection from a blood transfusion was 1 in 2,500. By the mid-1990s, the risk had decreased to only about 1 in 500,000. In February 2002, CBER licensed the first nucleic acid-based test for HIV and Hepatitis C virus, decreasing the risk further to only about 1 in 2 milllion. So, even though blood products are not completely risk-free, the risk of contracting HIV infection from receiving a blood transfusion is very small.

A New Era in Biologics

During the latter part of the 20th century, research in biotechnology and genetics revolutionized methods for making biologics. Additionally, advances in biotechnology led to the identification of many biological molecules important in disease processes, and thus to the identification of many potential new biological products. These new technologies and products raised important new regulatory challenges. Working with the broader scientific community, CBER scientists and physicians helped ensure that new production and testing methodologies were developed and implemented in a manner that produced safe, pure, and potent biologics. While leading to important further advances in vaccine development and blood safety, these advances also led to development of a range of biologic products that have made major contributions to all branches of medicine. Biologic therapeutics licensed in recent years have revolutionized the treatment of heart disease, cancer, serious infections, arthritis, anemia, hemophilia, multiple sclerosis, and many other diseases.

As the 21st century approached, CBER licensed a broad array of new biologic products. Examples of these products include new biotechnology-based drugs; new vaccines for typhoid, rabies, hepatitis A, and chickenpox; acellular pertussis vaccines, which cause fewer adverse side effects than whole-cell pertussis vaccines; and combination vaccines, such as the ones that protect against Haemophilus b disease, diphtheria, tetanus, and pertussis. During this time CBER also licensed the first HIV test system for which blood samples may be collected at home; a device that concentrates adult blood stem cells from bone marrow; and Rh_o (D) Immune Globulin Intravenous, the first human blood product approved for both intravenous and intramuscular use.



HIV virus
Courtesy of National Institutes of Health

The Biotechnology Revolution in Medicine

In recent years, biotechnology has facilitated the identification, development, and production of new biologic therapeutic products that have substantially advanced nearly all areas of medicine. The mortality rate due to heart attacks, a leading killer of Americans, was substantially reduced by the use of several fibrinolytic agents, licensed by CBER, that help clear clots from coronary arteries. An anti-platelet agent licensed by CBER, abciximab, has significantly reduced the morbidity from platelet aggregation that complicates many coronary procedures.

In oncology, biologic therapeutics have ushered in a new era of therapies that target specific tumor cells. Monoclonal antibodies including trastuzumab, which targets antigens on some breast tumors, and rituximab and alemtuzumab, which target antigens on some lymphomas and leukemias, have become valuable and important cancer therapies. Ibritumomab tiuxetan is the first CBER-approved biologic employing a monoclonal antibody to target a lethal radioisotope to a tumor. Biologic agents also have been critically important in adjunctive therapy of cancer patients. Colony stimulation factors, such as sargramostim and filgrastim, are used alone and with stem cell transplants, for example, bone marrow transplants, to increase white blood cell production and thereby decrease the risk of infections associated with cancer therapy. Erythropoietins regulate red blood cell production and have an important role in the treatment of anemia associated with renal failure or cancer.

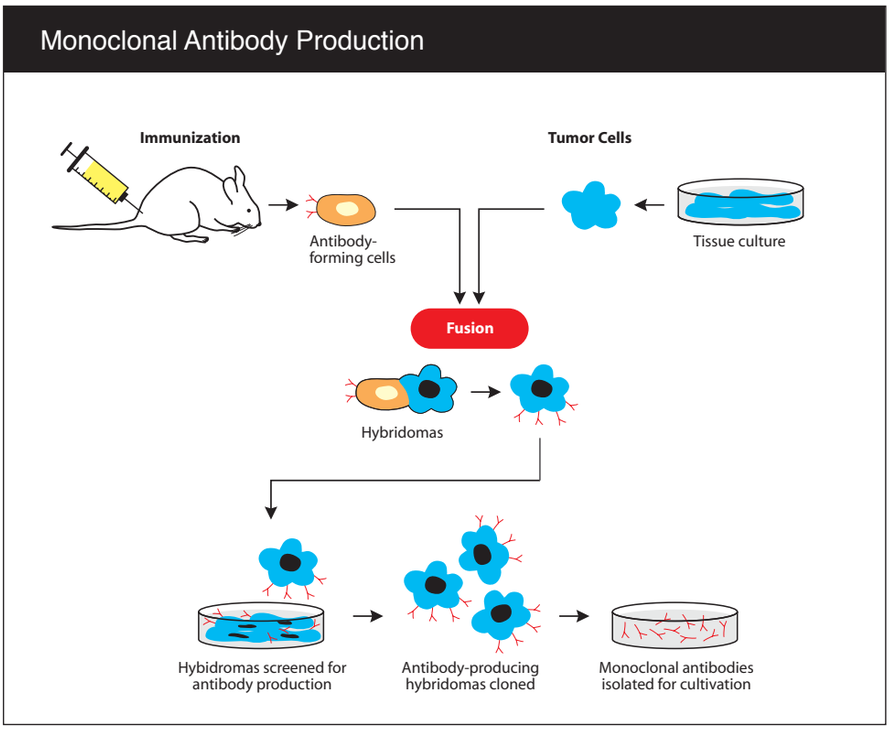
Treatment of rheumatoid arthritis, a debilitating disease, has been revolutionized by biologic agents that bind tumor necrosis factor, an endogenous substance involved in joint destruction. These and other anti-inflammatory agents are now under study for the treatment of many rheumatologic and autoimmune diseases. Antibodies that suppress immune responses by targeting T lymphocytes play an important role in preventing and treating rejection of organ grafts.

New biologics have provided benefits for patients with many previously untreatable diseases. Interferon beta products prevent exacerbations and slow progression of multiple sclerosis, and alteplase, a fibrinolytic agent, helps restore circulation to the brain in patients with stroke. Interferon alfa products were the first approved therapies for hepatitis C, an important cause of morbidity, and remain the backbone of therapeutic regimens for Hepatitis C.

Despite the use of antibiotics, severe sepsis has been fatal in more than 30% of cases. Drotrecogin alfa, a genetically-engineered activated protein C, is the first drug shown to reduce the mortality associated with the most severe forms of sepsis. Infliximab, an antibody against tumor necrosis factor, was the first therapy specific for Crohns' disease, an inflammatory bowel disease. Dornase alfa is an enzyme that helps clear the thick lung secretions that impair breathing in patients with cystic fibrosis. Interferon gamma is a cytokine that helps correct the immunodeficiency of chronic granulomatous disease, and delays disease progression in severe malignant osteopetrosis.

The Challenge of AIDS

The blood supply plays a vital role in the American health system. Almost four million Americans receive transfusions of blood products every year. The emergence of acquired immunodeficiency syndrome (AIDS) and discovery of the human immunodeficiency virus (HIV) that causes AIDS had serious implications for the safety of the U.S. blood supply. In August 1981, there were 108 reported cases of AIDS in the United States.



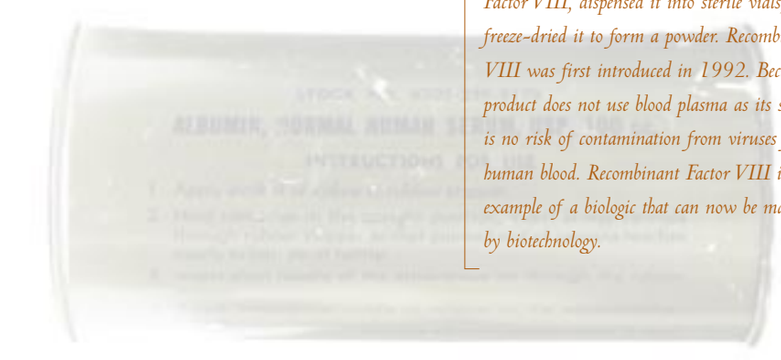
Between 1981 and December 2000, a total of 774,467 cases of AIDS were reported to CDC. The growing presence of AIDS and HIV meant that CBER had to protect the public against unsuitable blood and blood products by strengthening existing safeguards and developing new safeguards specific for HIV.

In 1985, soon after HIV was identified as the cause of AIDS, CBER licensed the first test kit to screen donated blood for HIV. As technology progressed, improved test kits were licensed and became available for use. In 1988, CBER started to inspect regulated blood and plasma donor facilities every year, rather than every two years. Today's general safety measures for protecting the U.S. blood supply include screening donors by interview, checking donors against a list of persons not eligible to donate blood, testing all blood donors for HIV, human T-lymphotropic virus (HTLV), hepatitis B and C, and syphilis before making the products available for use, and reviewing and monitoring any problems reported by blood establishments. As the operations of blood establishments have become more complex, CBER's oversight has adapted to the times. For example, CBER now regulates blood establishment computer software as a medical device, because of its critical role in managing and storing blood-related and donor-related information.

Quality control testing on blood grouping and typing reagents, 1967

The Recombinant Factor VIII Breakthrough

Factor VIII is a protein found in small quantities in the blood; it helps blood to clot. A deficiency of Factor VIII causes hemophilia A, a disease characterized by spontaneous bleeding that is difficult to control. Traditionally, human blood plasma was used as a source of Factor VIII concentrates used to treat hemophilia A. In 1984, however, scientists identified and isolated the gene—the part of human DNA—that contains the instructions for production of Factor VIII. Once they were able to copy this gene in the laboratory, it was possible to produce the Factor VIII protein by using a "recombination" process, referred to as recombinant DNA technology. Scientists linked the Factor VIII gene into a circular strand of DNA (a plasmid) and then inserted the plasmid into a nonhuman host cell that was very similar to a human cell and that was genetically engineered in the laboratory for this purpose. The plasmid moved to the host cell's nucleus, where genetic information is stored, and merged or recombined with the DNA already in the nucleus. Thus, the human Factor VIII gene became part of the host cell's genetic makeup. Host cells containing the Factor VIII gene were placed in a large vat called a bioreactor, and given nutrients to promote growth. As the cells grew, they produced Factor VIII. Scientists separated the Factor VIII from the host cells by using several purification steps. Finally, they sterilized the pure Factor VIII, dispensed it into sterile vials, and freeze-dried it to form a powder. Recombinant Factor VIII was first introduced in 1992. Because this product does not use blood plasma as its source, there is no risk of contamination from viruses found in human blood. Recombinant Factor VIII is one example of a biologic that can now be manufactured by biotechnology.

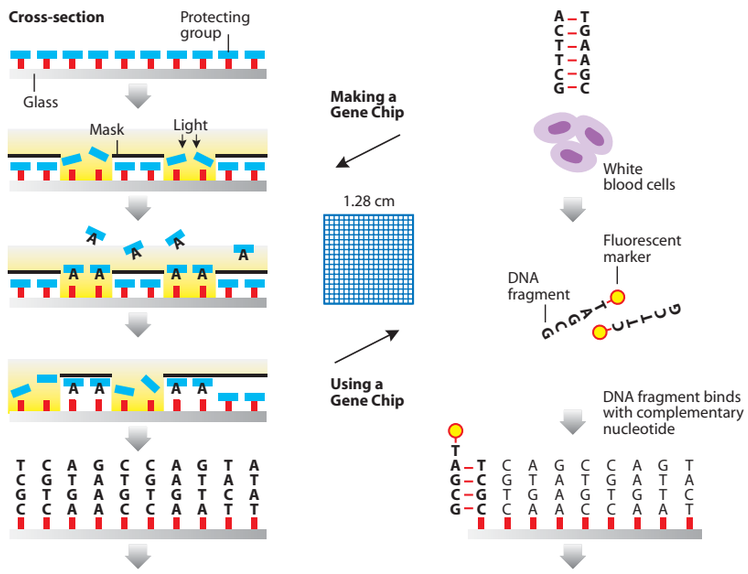


From the Bureau of Biologics to CBER

During the 1980s and 1990s, an unprecedented number of organizational changes took place in transforming the Bureau of Biologics to CBER. These changes all were aimed at achieving the most efficient regulation of rapidly-evolving biologic products. In 1982, the Bureau of Biologics was merged with the Bureau of Drugs to form the National Center for Drugs and Biologics (NCDB). In 1983, the biologics component of NCDB became the Office of Biologics Research and Review (OBRR) within the Center for Drugs and Biologics (CDB). It soon became clear that the regulatory programs for biologics and drugs could be managed more effectively if the programs were housed in separate organizations. So, in 1988, CDB was divided into two new Centers, CBER and the Center for Drug Evaluation and Research (CDER). At the close of the 1980s, it was evident that CBER's traditional workload of blood and vaccine products was changing to include biotechnology-derived products, as well as therapeutic products such as cytokines (non-antibody proteins that are part of the immune response to an antigen) and monoclonal antibodies (antibodies, for specific antigens of interest, produced by hybridoma clones grown in tissue culture). To streamline operations, CBER was reorganized in 1993 with separate program offices for vaccines, blood, and therapeutic products. Each office had both research and review responsibilities for their product areas. Also, separate offices were established to deal with manufacturer compliance and establishment licensing; these offices provided support to the product offices.

As a result of additional reorganizations since 1993, CBER now oversees biologics regulation through the coordinated efforts of eight offices: Office of Vaccines Research and Review, Office of Blood Research and Review, Office of Therapeutics Research and Review, Office of Cellular, Tissue, and Gene Therapies, Office of Compliance and Biologics Quality, Office of Communication, Training, and Manufacturers Assistance, Office of Biostatistics and Epidemiology, and Office of Management. In addition, the CBER Facility for Biotechnology Resources

Making a Gene Chip and Using a Gene Chip



(FBR) began operation in 1995. The FBR can be used by all CBER staff, and has the scientific expertise and sophisticated equipment needed to provide specialized reagents and services to CBER scientists and to support CBER's evaluation of methods used by biotechnology companies.

Also, CBER is part of the National Vaccine Program (NVP), created by Congress in 1986 to coordinate immunization activities. This program is a collaborative effort among all of the groups that have key roles in immunization, including federal agencies, the public, state and local governments, health care providers, and vaccine manufacturers. Major NVP goals are to develop and implement strategies for achieving the highest possible level of prevention of human diseases through immunization, as well as the highest possible level of prevention of adverse reactions to vaccines.

The Potential of Human Gene Therapy

Human gene therapy, an exciting and controversial area of biomedical research, refers to using normal genes or genetic material to either replace or cancel out defective genes in a person's body, in an effort to treat or cure the disease or medical condition caused by the defective genes. Gene therapy is likely to be most successful in diseases that are caused by defects in single genes—for example, hemophilia, cystic fibrosis, and hemoglobin disorders. Instead of giving Factor VIII, a protein that helps blood coagulate, to a person with hemophilia, it may be possible to replace the defective Factor VIII gene in the person's cells with a Factor VIII gene that works. The cells would then produce Factor VIII and the hemophilia would be cured. "Of course, that's a long way off," cautions Philip Noguchi, MD, Acting Director of the Office of Cellular, Tissue, and Gene Therapies at CBER, who also declares that such cures are "really the promise of what gene therapy hopes to offer."

Most current gene therapy research is being done using somatic cells (nonreproductive cells); the genes in these cells are not passed on to the next generation. NIH researchers W. French Anderson, MD, R. Michael Blaese, MD, and colleagues used the first approved gene therapy procedure to treat a four-year-old girl, in September 1990, and a nine-year-old-girl, in January 1991, both of whom had a disease called severe combined immune deficiency (SCID). This disease is caused by a gene defect that results in defective T cells, which are one type of white blood cells responsible for immunity. Children with SCID usually develop overwhelming infections and rarely survive to adulthood. The researchers removed T cells from the girls, grew the T cells in the laboratory, inserted the normal gene into the T cells, and then injected the genetically modified T cells into the girls' bloodstreams. This procedure strengthened the girls' immune systems, enough so that they had only an average number of infections and could attend public school. But, it was not a cure. The modified T cells only worked for a number of months, so the procedure had to be repeated periodically. This research illustrates just one way to replace defective genes; many other techniques can possibly be used and are being studied, as appropriate for the particular disease. As Dr. Noguchi explains, gene therapy techniques and vaccination techniques have something in common —"It is the whole idea of taking that which causes the disease, changing it into something that you can control, and using that entity itself to try to treat the disease." Gene therapy research is growing rapidly. Presently, CBER is overseeing more than 200 gene therapy studies, but has not yet licensed any human gene therapy product.

Fast Performance Liquid Chromatography for purification of recombinant proteins

Challenges for the 21st Century

Enormous challenges face CBER in its role as steward for the many diverse and innovative biological products, generated by combining biomolecular research and sophisticated technologies, that are being submitted by manufacturers for approval to enter the marketplace. More than 650 new biological products were developed in 2000, compared with 350 in 1990. More than half of the new products now being developed have their origin in biotechnology. In regulating new product areas, CBER's scientists must routinely develop appropriate laboratory and clinical methods to ensure the safety and effectiveness of new products. To do this, they must keep up to date with the rapid progress taking place in cutting-edge science. Even in older product areas, the technologies for production and testing continue to advance, and regulatory approaches must evolve to meet new challenges.

Challenging Areas of Research

Biomedical research areas that are receiving much attention include:

- **human gene therapy**—using normal genes or genetic material to either replace or cancel out the defective genes in a person's body that are responsible for a disease or medical problem

- **human cell and tissue transplantations**—for example, hematopoetic stem cell transplantation

- **xenotransplantation**—transplanting organs or tissues from animals into humans

- **emerging/re-emerging infectious diseases**—HIV, tuberculosis, Mad Cow

- **development of genetically-engineered (transgenic) plants and animals**—that are able to produce vaccines and drugs

- **production of vaccines and blood clotting factors**—from genetic material such as DNA

- **genomics**—the study of genes and their relationship to disease

- **proteomics**—the study of all proteins in living cells, especially protein changes in disease.

The rapidly growing number and variety of cellular and tissue-based products, and the regulation of these products will pose a continuous challenge for CBER in the 21st century. For many years, tissues have been transplanted in a wide range of procedures, such as skin replacement after severe burns, repair of injuries with tendons and ligaments, replacement of defective heart valves, restoration of eyesight using corneas, and use of human semen and implantation of eggs to help infertile couples have children. In recent times, scientists have developed innovative methods, some derived from biotechnology, that hold promise for enhancing and expanding the use of human cells and tissue in therapies for serious diseases and conditions such as cancer, diabetes, Parkinson's Disease, AIDS, hemophilia, and anemia. Existing cellular and tissue-based products and their potential uses are too diverse for a single set of regulatory requirements to be appropriate for all. Therefore,

Emmanuel F. Petricoin, PhD
CBER

Lance A. Liotta, MD, PhD
National Institutes of Health

The NCI-CBER/FDA Clinical Proteomics Program

Proteomics is the study of all proteins in living cells. A new program, the Clinical Proteomics Program, announced in July 2001 by the Food and Drug Administration (FDA) and the National Cancer Institute (NCI), will apply proteomics directly to patient care. Led by Lance Liotta, MD, from NCI's Center for Cancer Research, and Emmanuel Petricoin, PhD, from CBER, the Program will use new, powerful technologies in an innovative approach that could possibly revolutionize cancer detection and care. Liotta and Petricoin have identified more than 130 proteins in cells of the breast, ovary, prostate, and esophagus that change in amount when the cells grow abnormally. This information may help to provide new ways of diagnosing and treating cancer in earlier stages of the disease, when there often is a better chance of cure. Specialized equipment was developed in Liotta's laboratory that can scan cells for hundreds of proteins at once and generate protein "fingerprints" for the cells. The scientists are analyzing protein patterns in normal and precancerous cells to find clues about why and how precancerous cells develop, and are examining tumor cells before and after treatment to determine how the treatment affects cell protein patterns. In addition, they are looking for protein patterns in blood that might signal the presence of cancer. In February 2002, the researchers reported that, using a special computer program, they have been able to recognize blood protein patterns that readily distinguish between women with and without ovarian cancer; they correctly identified 50 out of 50 ovarian cancer patients and 63 out of 66 women without cancer. An exciting finding in this study was the ability to correctly identify early-stage ovarian cancer, difficult to detect by other means. Currently, four out of five ovarian cancer patients are diagnosed at a late stage of disease; these women have, at best, only a 20 percent chance of living for five years after diagnosis, compared with 95 percent for women who are diagnosed with early-stage disease. In addition to diagnosing cancer, and possibly other diseases, at earlier stages than is now possible, potential benefits of the Clinical Proteomics Program include: developing individualized treatments that have been predetermined to be effective for the patient; determining toxic side effects and beneficial effects of treatments in the laboratory before using them on patients; and improving the understanding of tumors at the protein level, leading to development of better treatments. Clinical trials using proteomics to help make decisions about patients' experimental treatments have begun recently as part of this "bench-to-bedside" clinical research program. According to Dr. Petricoin, proteomics could "change the shape of how medicine is practiced."

CBER has developed a new framework for cell and tissue regulation that will provide a unified approach to the regulation of both traditional and new products. CBER's goal is twofold: to ensure that innovation and product development can proceed in the rapidly growing area of cell and tissue research without being hindered by excessive regulation, and to ensure that cell and tissue-based products provide the assurance of safety that the public has come to expect from products regulated by CBER.

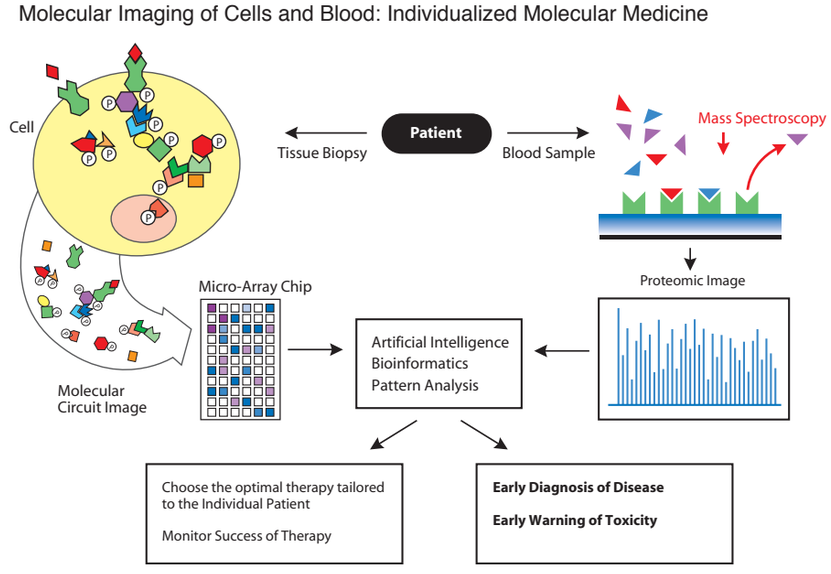
Vaccine research and regulation also will continue to be a challenge in the 21st century. At the end of the 20th century, the number of new technologies available for making vaccines increased dramatically, building on rapid advances in many areas, including molecular biology, recombinant DNA technology, polysaccharide chemistry, protein chemistry, purification methods for large molecules, analytical techniques, virology, bacteriology, and immunology. As a result, CBER must regulate a wide variety of vaccine types, ranging from vaccines made by using the whole cell of an organism to vaccines that are essentially pure chemicals.

New microorganisms are constantly emerging and known microorganisms are constantly changing. Emerging infectious diseases—those that have newly appeared or have existed but are rapidly increasing in incidence or geographic range—include tuberculosis, malaria, hepatitis C, Lyme disease, AIDS, hantavirus pulmonary syndrome, ebola, and West Nile virus disease, among others. Vaccines have yet to be produced for many of these diseases. Even influenza can be considered an emerging infectious disease, because influenza viruses change from year to year. The effort to protect people against new and changing infectious microorganisms is "a never-ending battle," according to Neil Goldman, PhD, CBER's Associate Director for Research.

Mad Cow Disease

The scientific name for "mad cow disease" is bovine spongiform encephalopathy (BSE). BSE belongs to a group of diseases called transmissible spongiform encephalopathies (TSEs). There are no validated treatments or preventive vaccines for TSEs; they appear to be invariably fatal. In these diseases, which occur in both animals and in people, the brain develops a sponge-like appearance. Also, a unique abnormal form of a normal protein called the prion protein is found in the brain tissues. Abnormal prion proteins are believed by many authorities to be the agents that cause TSEs, but little is known about how they work. TSEs can be transmitted between animals, for example, cow-to-cow or sheep-to-cow, and between animals and humans. BSE was discovered in cattle in the United Kingdom in the mid-1980s. It appears that the disease was spread by feeding cattle with supplements containing infected animal tissues and byproducts. In 1996, a new kind of TSE was found in people in the United Kingdom; this disease is now called vCJD because it is a variant of Creutzfeldt-Jakob disease (CJD), a known TSE that affects people worldwide, about one case per million people each year. Investigation revealed that the likely cause of vCJD in people was eating contaminated beef products made from cattle with BSE. At present, more than 115 people in Europe, mostly in the United Kingdom, have died from vCJD. It can take many years for symptoms of vCJD to become noticeable, so it is not known how many more people may be infected with the disease agent. TSE agents are exceptionally resistant to destruction. They are not completely destroyed by the same methods that destroy bacteria and viruses. Fortunately, there is no evidence of either BSE or human cases of vCJD contracted in the United States. As part of its mission to protect the public, CBER is evaluating methods for preventing exposure of Americans to agents of these diseases, especially as a result of blood transfusions or tissue transplantation.

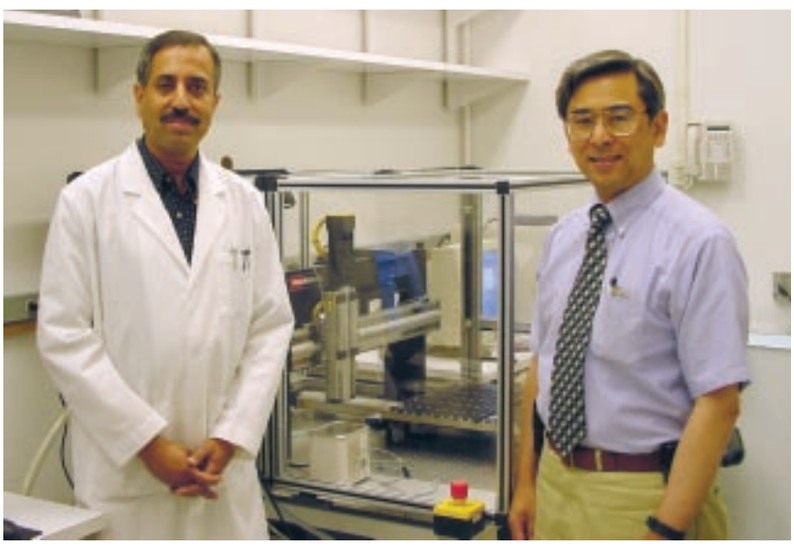
FDA-NCI Clinical Proteomics Program



Innovative vaccine research is making progress in the development of "edible vaccines" and genetic (DNA) vaccines. Both edible vaccines and genetic vaccines have several advantages over traditional vaccines. They are unable to cause infection, are relatively easy to generate in large quantities, and are stable during storage. Edible vaccines are produced by genetically altering the edible parts of plants. Antigens have been produced in plants for rabies (in tomato), Norwalk virus (in potato), hepatitis B virus (in potato), and cholera (in potato), and testing in humans is under way. Banana is being investigated as a possible vaccine delivery food because it can be eaten raw and appeals to children.

Most genetic vaccines being investigated are made using DNA. Many of these vaccines consist of plasmids (small rings of DNA) that have been altered to carry genes that specify one or more antigens made by the disease-causing organism. The vaccines can be delivered by injection. Once inside the body's cells, the plasmids travel to the cell nucleus and instruct the cell to produce the antigens. Then, these antigens trigger the body's immune system.

Cancer vaccines are another promising area of vaccine research. There are various tumor-associated antigens (TAAs) present on tumor cells that are absent or present in only very small amounts on normal cells. One example is carcinoembryonic antigen (CEA), produced by colon, breast, lung, gastric, and pancreatic cancers. When used to vaccinate cancer patients, the TAAs can elicit a response from the immune system that is directed at the tumor cells. Some gene therapy studies involving cancer are actually based on the principle of cancer vaccines. Researchers have introduced genes that code for immune hormones into tumor cells to make the cells more reactive to the patient's immune system.



Raj K. Puri, MD, PhD, and Philip D. Noguchi, MD, CBER, conduct DNA analyses on microarray system

The new analytical methods of DNA microarray technology, which provide scientists with information on thousands of genes simultaneously, and proteomics, the study of all proteins in living cells, are powerful new research tools. They have tremendous potential for clarifying the complex causes of infectious disease, providing new diagnostic tests, contributing to the discovery of innovative medicines and vaccines, and assisting in the standardization of biologics. Because of advancements in genomics and proteomics research and technology, it is likely that biologics in the 21st century will be tailored on a molecular basis.

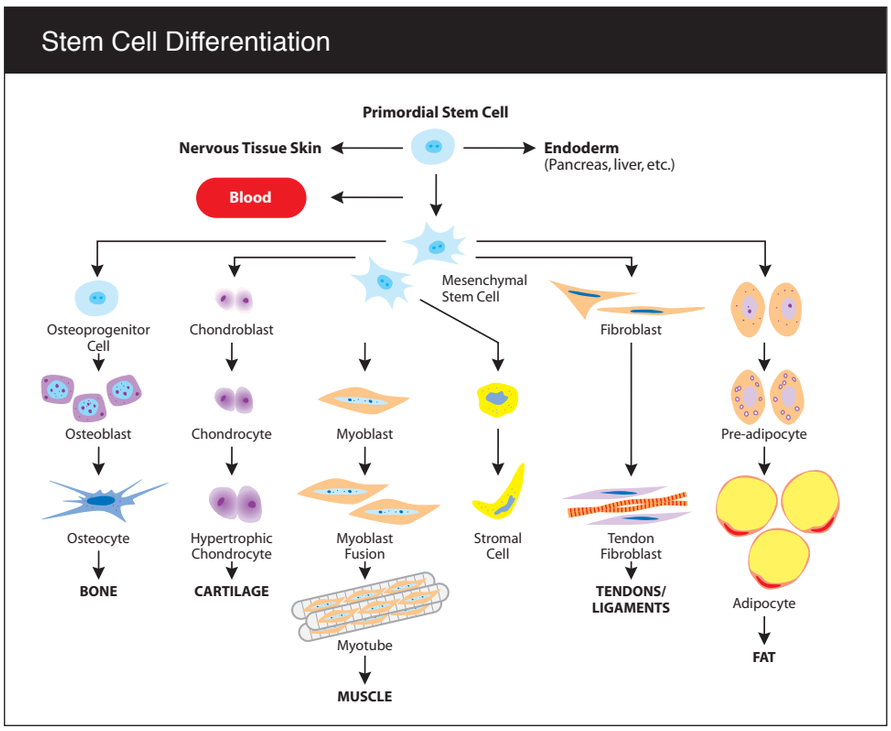
Ethical Concerns

Several current clinical research areas have raised ethical and societal concerns that lie outside of CBER's primary responsibility for safety, purity, potency, and efficacy of biologicals. For example, many believe that gene therapy is acceptable if applied to somatic (nonreproductive) cells, but are less willing to accept gene therapy if applied to germ (reproductive) cells, because germ cells carry the genes that are passed on to the next generation. Others believe that any kind of gene manipulation is wrong, including development of genetically engineered plants and animals, because of possible unforeseeable long-term effects that may be harmful to either human health or the environment. Stem cell research using human embryos also has raised concerns. A stem cell is a human cell that may be derived from an embryo, fetus, or adult. Human embryonic stem cells are unique in that they are capable of continuous self-renewal and have the ability to give rise to most cell types that constitute the human body. It is important that research using human embryonic stem cells proceed responsibly and ethically, especially when used in clinical trials. Xenotransplantation also has raised ethical dilemmas because of the risks of transmitting infectious agents from animals to humans, particularly certain viruses that may remain inactive or hidden for many years before they cause disease. Ethical and societal issues such as these lie beyond CBER's legal responsibility. However, CBER clearly has a role to play in the public discussion of these issues. For example, CBER has *ex officio* membership on the NIH Recombinant DNA Advisory Committee (RAC) and the HHS Secretary's Advisory Committee on Xenotransplantation (SACX). CBER has restructured its own Biological Response Modifiers Advisory Committee (BRMAC) to discuss issues such as the above in the context of clinical trials using experimental products. CBER is committed to continued public participation in discussions of novel products that have enormous potential clinical impact, yet also present novel ethical issues.

Stem Cell Research

Stem cell research is creating great excitement among scientists because of its potential for developing new ways to prevent and treat disease. Stem cells are cells that grow well in the laboratory and can differentiate into specialized cells for practically every kind of tissue in the body—for example, skin cells, heart muscle cells, or blood cells. Stem cell research is important to science and to advances in health care for several reasons. Understanding how stem cells differentiate can help scientists understand why cells sometimes develop in abnormal ways, as in cancer or birth defects. Also, stem cell lines could be used to test the safety and effectiveness of new drugs before the drugs are tested in animals and people. Finally, and perhaps most important, stem cells could be stimulated to change into specialized cells that could be used for "cellular therapies." The specialized cells could be used to treat diseases and conditions such as Parkinson's and Alzheimer's diseases, spinal cord injury, burns, heart disease, diabetes, and arthritis. For example, in diabetes, specialized cells in the pancreas called islet cells cannot make insulin normally, so insulin injections are needed. Now, there is evidence that if "good" islet cells are transplanted into the pancreas, enough insulin is produced so that injections become unnecessary. Currently, stem cell products are regulated by CBER as biologics. As stem cell research continues, CBER will continue to develop standards and regulations appropriate for stem cell products.

Konstantin M. Chumakov, PhD, CBER, conducts MAPREC research on polio vaccine



Quality and Safety Issues

Quality and safety issues related to biologics will continue to have high priority in the 21st century. For instance, the need to identify, detect, and either remove or inactivate harmful, infectious agents (such as bacteria, viruses, or parasites) in biological products will remain a challenge. Fortunately, the availability of sophisticated analytical tools is making it easier to identify and detect contaminants, and to characterize products. An example is the "mutant assay by polymerase chain reaction and restriction enzyme cleavage" (MAPREC) that was developed at CBER. This assay can detect a specific molecule in the poliovirus that determines whether the virus will cause the paralytic form of polio. The assay is being made part of the World Health Organization's testing requirements for live oral polio vaccine to help ensure a consistently safe vaccine.

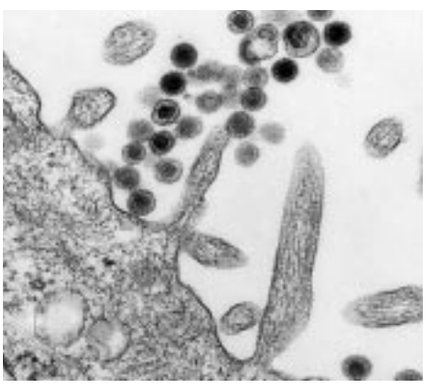
The public wants quick translation of biomedical discoveries into biological products. The need to develop standards for licensing new biologics that ensure that new products are safe, pure, potent, and effective, and are produced according to current good manufacturing practices—while meeting the demand for rapid availability—will be a continual challenge for CBER.

Global Considerations

The world-wide elimination of smallpox in the late 1970s was a major victory for international public health efforts. However, there is much more work to be done on the global scale. For instance, elimination of paralytic polio in all countries presents technical and logistical challenges. Also, safe and effective vaccines that can be used in global immunization efforts to prevent major infectious diseases such as tuberculosis, malaria, and AIDS are urgently needed, but are difficult to devel

op. Even if safe and effective vaccines for these diseases become available, the process of making the vaccines accessible for everyone, especially in developing countries, will be fraught with major challenges, both fiscal and logistical. Public health organizations worldwide, including CBER, will be working to meet such challenges.

International harmonization of regulatory requirements for medicinal products, including biologics, is essential. Without harmonization, different technical requirements among countries make it necessary for industry to conduct numerous similar tests on new products before the products can be marketed internationally. This increases the time that it takes to move discoveries from the laboratory to products that benefit the public. Since 1990, the International Conference on Harmonisation has coordinated international efforts to achieve common or compatible approaches to regulation. CBER takes part in numerous international harmonization activities in the areas of developing international standards, providing technical assistance, providing education and information, and participating in the development of trade policy and free trade agreements. The Center will continue to take an active role in addressing challenges presented by the harmonization of biologics regulation in the 21st century.



Porcine Endogenous Retrovirus (PERV) isolated in fresh pig lymphocytes by Carolyn Wilson, PhD, and colleagues at CBER

Xenotransplantation

Xenotransplantation is any procedure in which live cells, tissues, or organs from a nonhuman animal source are transplanted, implanted, or infused into a human. In addition, procedures that use human body fluids, cells, tissues, or organs that have had contact with live nonhuman animal cells, tissues, or organs are defined as xenotransplantation. The increasing interest in xenotransplantation is partly because the demand for human organs for transplantation is much greater than the supply. Today, in the United States, 13 patients die each day while waiting for organ transplants. Also, evidence suggests that transplantation of cells and tissues may be beneficial for certain diseases—for instance, epilepsy, diabetes, and degenerative neurological diseases such as Parkinson's disease—and human cells and tissues are not usually available. Although the potential benefits of xenotransplantation are great, there are also risks. For example, animal cells, tissues, or organs might harbor infectious agents such as bacteria or viruses that could cause disease in the transplant recipient and/or contacts of the recipient. Philip Noguchi, MD, Acting Director of the Office of Cellular, Tissue and Gene Therapies at CBER, emphasizes that in xenotransplantation, "the first question is, how do you test for what's infectious?" Some infectious agents may remain dormant for many years, before they finally cause noticeable disease. Further, an infectious agent that does not cause disease in an animal may cause serious disease in a human transplant recipient or even be fatal. Research conducted at CBER has been important for understanding the safety issues associated with xenotransplantation. CBER scientists are conducting studies on known and emerging infectious agents, and on problems related to organ and tissue rejection that need to be solved before xenotransplantation products can be used safely and effectively.

Countering Bioterrorism

CBER has had, and will continue to have, a key role in countering bioterrorism. The Center is responsible for the development and licensing of biological products to prevent, diagnose, and treat outbreaks from exposure to pathogens that have been identified as possible biological warfare agents. CBER staff must guide these products through the review and approval process before marketing is permitted. CBER coordinates its activities in countering bioterrorism with those of the Department of Defense and other components of the Department of Health and Human Services. Developing effective means that can be quickly put into use to protect the public against bioterrorism in the 21st century is critical.

Conclusion

If Joseph Kinyoun, the first director of the Hygienic Laboratory, could view CBER now, he might consider it to be a creation of science fiction—the changes in technology during the 20th century have been that remarkable. But then again, he might merely smile and reflect on CBER's remarkable achievements and on how the Biologics Control Act, and the union of scientific research, law, and regulation, have made CBER what it is today.

Although today's thoroughly modern CBER bears little physical resemblance to the modest Hygienic Laboratory of the late 19th century, its approach to protecting the public health is just the same as that used by the Hygienic Laboratory and the other organizations that were part of the evolution leading to CBER. This approach, based on science and law, has succeeded admirably over the past 100 years and provides the bedrock foundation for CBER's march into the next century.

Dr. Zoon predicts, "The next century will be very exciting and very challenging. There will be an explosion of new products—new drugs, new therapies—even cures, that, until recently, were only the dreams and aspirations of physicians and scientists. In the next 100 years, or sooner, we can expect to have an AIDS vaccine, a safer blood supply, perhaps synthetic blood, and safer tissue products. Advances in tissue engineering will lead to bio-engineered replacement parts. We will have new and more effective treatments for cancer, Alzheimer's, and other devastating diseases. The fruits of proteomics and genomics research will produce customized medicines that have maximum therapeutic benefit and less harmful side effects.

Our biggest challenge will be to make sure that when we repair, replace, restore, or regenerate normal body function, we do so in the safest, most effective, and most ethical way possible. In the last ten years, CBER has laid the groundwork to meet the regulatory challenges posed by these new and potentially profound biomedical discoveries. CBER's role in the next 100 years is to continue to advance the public health, do the very best job it can, involve the public, and always do the right thing. We welcome the future and look forward to continuing to fulfill our mission to protect and enhance the public health."

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Acronyms Used in this Publication

BCA	Biologics Control Act of 1902
BOB	Bureau of Biologics
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
DBC	Division of Biologics Control
DBS	Division of Biologics Standards
FDA	Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act of 1938
LBC	Laboratory of Biologics Control
MHS	Marine Health Service
NFIP	National Foundation for Infantile Paralysis
NIH	National Institute(s) of Health
NMI	National Microbiological Institute
PHS	Public Health Service
PH-MHS	Public Health and Marine Hospital Service
WHO	World Health Organization

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