

BIOLOGICS - CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

	FY 2004 Actuals	FY 2005 Enacted ^{1/}	FY 2006 Estimate	Increase or Decrease
Program Level	\$148,391,000	\$151,478,000	\$158,038,000	+\$6,560,000
<i>Total FTE</i>	797	815	801	-14
Budget Authority	\$103,537,000	\$102,869,000	\$102,132,000	-\$737,000
<i>GSA Rent and Rent Related</i>	7,272,000	5,979,000	\$6,039,000	+\$60,000
<i>Administrative Efficiencies</i>	N/A	N/A	-\$132,000	-\$132,000
<i>IT Reduction</i>	N/A	N/A	-\$665,000	-\$665,000
<i>Total FTE</i>	559	565	548	-17
User Fees	\$44,854,000	\$48,609,000	\$55,906,000	+\$7,297,000
<i>PDUFA</i>	\$41,181,000	\$40,214,000	\$46,838,000	+\$6,624,000
<i>MDUFMA</i>	\$3,673,000	\$8,395,000	\$9,068,000	+\$673,000
<i>Total FTE</i>	238	250	253	+3

ORA Estimate	\$31,076,000	\$32,541,000	\$33,330,000	+\$789,000
<i>Budget Authority</i>	\$30,021,000	\$29,992,000	\$30,052,000	-\$60,000
<i>FTE</i>	233	216	206	-10
<i>User Fees</i>	\$1,055,000	\$2,549,000	\$3,278,000	+\$729,000
<i>FTE</i>	8	14	14	0

Includes structure changes to FDA's budget, which displays GSA and Other Rent and Rent Related Activities in the Program line, and the Office of Regulatory Affairs as its own program. ORA estimates are for information purposes only and are not included in the Center program level total.

^{1/}Contains budget authority rescission of 0.8 percent.

Historical Funding and FTE Levels

Fiscal Year	Program Level	Budget Authority	User Fees	Program Level FTE
2002 Actual ^{1/}	\$149,311,000	\$111,054,000	\$38,257,000	894
2003 Actual	\$165,558,000	\$117,391,000	\$47,116,000	975
2004 Actual	\$148,391,000	\$103,537,000	\$44,854,000	797
2005 Enacted	\$151,478,000	\$102,869,000	\$48,609,000	815
2006 Estimate	\$158,038,000	\$102,132,000	\$55,906,000	801

Does not contain GSA Rent or Other Rent and Rent Related Activities.

^{1/}Includes FDA's FY 2002 Appropriation and the Counterterrorism Supplemental.

STATEMENT OF BUDGET REQUEST

The Biologics Program is requesting \$158,038,000 for its mission activities including:

- To ensure the safety, efficacy, potency and purity of biological products including vaccines, cells, tissues, gene therapies, and related drugs and devices intended for use in the prevention, diagnosis and treatment of human diseases, conditions or injuries;
- To ensure the safety of the nation's supply of blood and blood products;
- To evaluate the safety and effectiveness of biological products before marketing, and monitors the pre-clinical and clinical testing of new biological products;
- To license biological products and manufacturing establishments, including plasmapheresis centers, blood banks, and vaccine manufacturers; and,
- To conduct regulatory research to establish product standards and develop improved testing method

PROGRAM DESCRIPTION

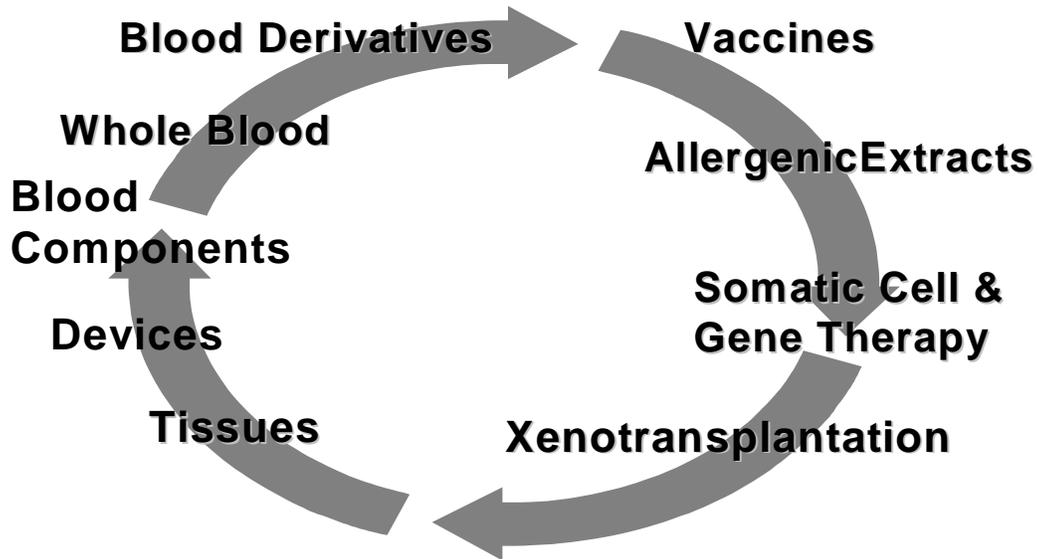
The Biologics Program regulates products that are on the leading edge of technology. Rapid scientific advances in biochemistry, molecular biology, cell biology, immunology, genetics, and information technology are transforming biological product discovery and development, paving the way for unprecedented progress in developing new medicines to conquer disease.

While scientific advances of new biological products promise great health benefits for U. S. consumers, FDA must ensure that these products are safe and effective. FDA is also responsible for ensuring the safety of the nation's blood supply by minimizing the risk of infectious disease transmission and other hazards, while facilitating the maintenance of an adequate supply of whole blood and blood products.

ORA supports CBER by conducting premarket activities such as: bioresearch monitoring of clinical research, preapproval inspections and laboratory method validations needed for premarket application decisions, and inspecting manufacturing facilities to ensure their ability to manufacture the product to the specifications stated in the application. The Field conducts risk-based domestic and foreign postmarket inspections of medical products to assess their compliance with Good Manufacturing Practice requirements.

Besides overseeing regulated products on a surveillance or "for cause" basis, ORA staff also respond to emergencies and investigate incidents of product tampering and terrorist events or natural disasters. To complement the regular field force, the Office of Criminal Investigations investigates instances of criminal activity in FDA regulated industries. In FY 2006, ORA will expend an estimated \$33,330,000 in support of the Program.

BIOLOGICAL PRODUCTS REGULATED BY CBER



PERFORMANCE ANALYSIS

During the latest completed performance period, (FY 2003), CBER successfully achieved the targets for all four performance goals. Data for FY 2004 will be available later in FY 2005. For more detailed explanation of these goals and results, please see their respective section contained in the Detail of Performance Analysis under the Supporting Information tab.

The performance targets for implementing the Prescription Drug User Fee Act (PDUFA III) are very high. To sustain these ambitious targets, adequate funding must be assured. Since the PDUFA fee structure is predicated on supplementing existing appropriated funding, the request must be designed to ensure that budgetary authority and user fees are adequate.

Performance Highlight:

Goal Target	Context	Results
Review and act upon 90% of standard original PDUFA NDA/BLA submissions within 10 months; and review and act on 90% of priority original PDUFA NDA/BLA submissions within 6 months of receipt.	To provide the U.S. public with quicker access to new biologics, FDA consults closely with product sponsors early in product development and makes prompt decisions on important new biological product applications.	Since 1994, FDA has met or exceeded performance goals of completing review and action on 90% of standard original PDUFA NDA/BLA submissions within 10 months; and reviewing and acting on 90% of priority original PDUFA NDA/BLA submissions within 6 months of receipt.

RATIONALE FOR BUDGET REQUEST

This request, for Budget Authority and User Fees, supports various activities that contribute to the accomplishment of program outputs and performance goals, and presents FDA's justification of base resources by strategic goals.

PROGRAM RESOURCE CHANGES

Program Account Restructuring

GSA Rent and Other Rent Activities Structure Change

To provide increased flexibility and accountability, eliminate the need for the many reprogramming requests to Congress, place accountability for rental costs within the operating program, would better reflect the total cost of each program. This budget changes the way the GSA Rent and Other Rent-Related Activities budget lines are displayed by incorporating these resources into the Biologics Evaluation and Research program level requests.

Office of Regulatory Affairs (ORA) Estimate and Structure Change

This budget also establishes a single budget line item for the ORA. To help the field program provide service more effectively, especially by providing much needed flexibility to respond to shifting program priorities. This additional flexibility is essential to allow FDA to respond to emerging situations without being hindered in performing its mission critical activities. These activities have been removed from each program line and the Field estimates will be provided under the Office of Regulatory Affairs to reflect the planned spending for each program area.

Budget Authority

GSA Rent +\$60,000

To help meet the rising costs of GSA rent, a total increase of \$4,100,000 is requested, of which \$60,000 is for the Center for Biologics Evaluation and Research. This increase will help cover inflation on FDA's current GSA-leased facilities.

Management Savings: -\$797,000 and -3 FTE

FDA will reduce spending on administrative and IT activities. Specifically, these reductions are:

- **Administrative Efficiencies: -\$132,000 and -1 FTE**
Administrative efficiency savings will total -\$1,554,000 and -15 FTE, of which the CBER share is -\$132,000 and -1 FTE.
- **Information Technology Reduction: -\$665,000 and -2 FTE**
IT reductions will total -\$5,116,000 and -15 FTE, of which the Center for Biologics Evaluation and Research share is --\$665,000 and -2 FTE.

User Fees

Prescription Drug User Fee Act (PDUFA): +\$6,624,000 and +2 FTE

PDUFA authorized the FDA to collect fees from the pharmaceutical industry to augment appropriations spent on drug review. These fees expand the resources available for the process of reviewing human drug applications including reviewers, information management, space costs, acquisition of fixtures, furniture, equipment and other necessary materials so that safe and effective drug products reach the American public more quickly. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 reauthorized the collection of user fees to enhance the review process of new human drugs and biological products and established fees for applications, establishments, and approved products. These amendments are effective for five years and direct FDA to strengthen and improve the review and monitoring of drug safety; consider greater interaction with sponsors during the review of drugs and biologics intended to treat serious diseases and life-threatening diseases; and develop principles for improving first-cycle reviews. The increases will contribute to meeting these mandated directives.

Medical Device User Fee and Modernization Act (MDUFMA): +\$673,000 and +1 FTE

MDUFMA is patterned after the successful Prescription Drug User Fee Act, a successful partnership between the Federal government and stakeholders to improve the quality and timeliness of the medical device review process. This multi-year effort authorizes the collection of user fees from those who submit premarket applications, certain supplements to those applications, and premarket notifications. The funds continue the following FDA efforts begun in FY 2003 including:

- Acquire and train staff to meet a set of aggressive performance goals, for expediting the review of medical device applications;
- Promote public health with major improvements in review of expedited medical devices; and,

- Make major improvements in review performance in areas where fees are collected, while maintaining performance in other areas.

JUSTIFICATION OF BASE

Protecting and promoting the public health in the 21st Century is a great responsibility. Mastering it requires meeting some unprecedented challenges: having a strong organization that attracts and retains the most talented scientists; utilizing dynamic and responsive regulation for new and better ways to reduce risks; promoting quick access to needed new medical technologies that are safe and effective; helping to assure the continuing safety and availability of regulated products; helping consumers get true and useful information about the products they use; and facilitating quick responses to the challenges of bioterrorism as well as emerging infectious diseases. These are among the many critical challenges we face. The Program can and will continue to play both a facilitating and a leadership role in meeting these challenges, seeking input from, and effective collaboration with our partners.

The Program is responsible for addressing regulatory challenges related to ensuring the safety and efficacy of a wide range of biological products including blood and blood products, human tissue, cell and gene therapies, vaccines, and allergenic products. Meeting these challenges successfully will require knowledge and utilization of scientific advances in areas such as proteomics, genomics and gene therapies, xenotransplantation, new vaccine technologies and delivery methods, and novel cellular and tissue therapies. In these and other areas, CBER research, often performed in collaboration with partners in government, academia and industry, helps to identify opportunities to advance new and emerging technologies, providing needed standards, assays and models to better measure and assure product safety, efficacy and consistency. These contributions help to more safely and efficiently move innovative products along what has been termed the “critical path” to availability for patients who can benefit from them. The Program will continue to further sharpen its focus, and seek continuing input and collaboration, in utilizing its scientific resources and expertise to facilitate the development of products that are safe and effective – consistent with FDA’s Critical Path Research Initiative (<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>).

Research Support for Product Development



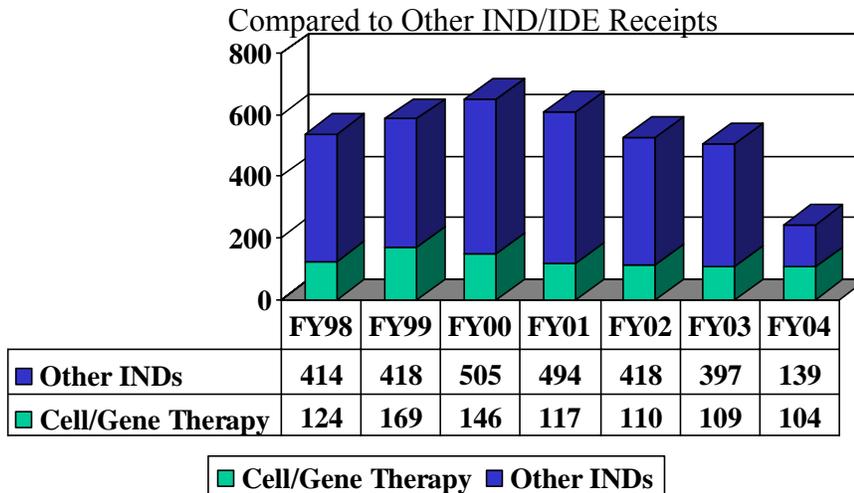
USING RISK-BASED MANAGEMENT PRACTICES

Base resources will be used to conduct science-based risk management in all Agency regulatory activities so that the Agency’s limited resources can provide the most health promotion and protection at the least cost to the public. These activities include the efforts discussed below.

Gene Therapy

One of the most exciting and highly publicized areas in biomedical research today is human gene therapy – the replacement of a person’s faulty genetic material with normal genetic material to treat or cure a disease or abnormal medical condition. Over time and with proper oversight, this may become an effective weapon in modern medicine’s arsenal to help fight diseases such as cancer, diabetes, high blood pressure, heart disease and other genetic disorders.

CBER GENE THERAPY/SOMATIC CELL INDs RECEIVED



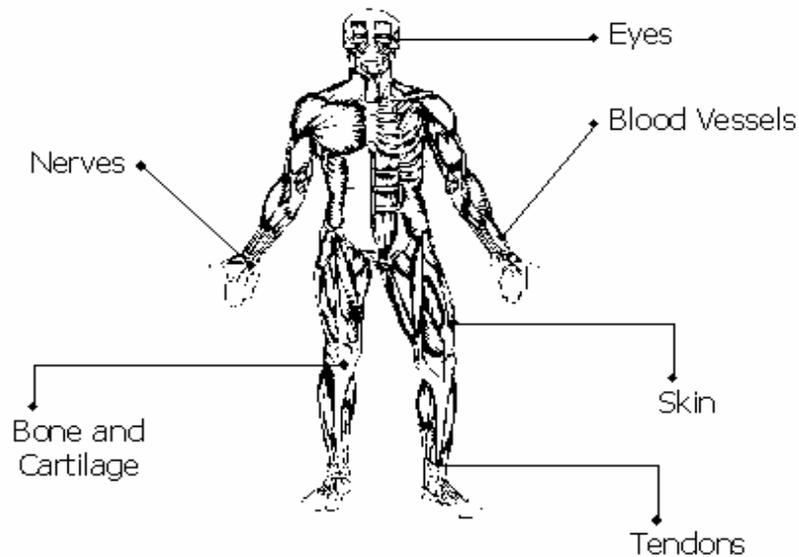
While FDA has not yet approved any human gene therapy products for marketing, gene-related research and development is continuing to grow and FDA is very involved in overseeing this activity. Since FY 2000, FDA has received over 400 requests from medical researchers and manufacturers to study gene therapy and to develop gene therapy products. Presently, FDA is overseeing approximately 230 active investigational new drug gene therapy studies.

Human Cells, Tissues and Cellular Based Products

The term “human cells, tissues, and cellular and tissue-based products (HCT/P’s)” covers many products transplanted for medical uses, such as skin replacement following severe burns, tendons and ligaments to repair injuries, bone replacement, and corneas to restore eyesight. In this rapidly growing industry, the number of musculoskeletal tissue transplants increased from approximately 350,000 in 1990 to over 1 million in 2004. Over the past decade advancing technology and improved techniques have expanded the therapeutic uses of tissue-based products.

FDA seeks to accomplish three primary goals with respect to human tissues while not discouraging the development of new products: (1) to prevent the spread of communicable diseases; (2) to ensure that safety and efficacy are demonstrated for cellular and tissue-based products that are also drug, biological, and medical device products; and, (3) to help enhance public confidence in these products so that, where appropriate, they can fulfill their great potential for improving and saving lives.

HUMAN TISSUES AND CELLS



This diagram shows the various human tissues and cells used in transplantation.

Improvements in Tissue Technologies and Donor Eligibility

- *Implemented a comprehensive approach for regulating new tissue technologies that have future potential to provide treatment for such diseases as cancer, Parkinson's Disease, hemophilia and other serious conditions.*
- *Implemented establishment registration and product listing for all HCT/P establishments, and recently implemented a new web-based registration process.*
- *Published a new final rule establishing good tissue practices, which includes the methods, facilities and controls used to manufacture these products. It requires manufacturers to recover, process, store, label, package and distribute human cells, tissues and cellular and tissue-based products in a way that prevents the introduction, transmission, or spread of communicable diseases. The regulations apply to a broad range of these products including musculoskeletal tissue, corneas, human heart valves, dura mater (lining of the brain) and cellular therapies. This new rule, which applies to all non-reproductive cells and tissues, will become effective on May 25, 2005.*
- *Two other related proposed rules have been finalized, including the rule regarding establishment registration and listing was (January 19, 2001) which requires tissue facilities to register with FDA and list their product, and the rule, regarding donor suitability finalized on May 25, 2004, which focuses on donor screening and testing measures to prevent the unwitting use of contaminated tissues with potential to transmit infectious diseases. It will become effective on May 25, 2005, and applies to all HCT/Ps, including reproductive cells and tissues.*

Pandemic Influenza

Preparation for the next pandemic of influenza requires action in the inter-pandemic period, including the production of vaccines, which is unique among vaccine products in that the viruses are changed on a frequent basis and the time available for making and distributing each year's new vaccine is fixed at 6 to 8 months. CBER scientists:

- Actively advise national and international public health groups such as WHO, CDC, NIH, and the National Vaccine Program Office on selecting new influenza viruses to be used in annual vaccine production and in preparing for an influenza pandemic. Every year, CBER's Vaccines and Related Biological Products Advisory Committee makes recommendations for the strains to be used in making influenza vaccines and informs manufacturers of the choices. These recommendations are based on data provided from laboratories worldwide as the strains are continuously evolving or mutating. As soon as strains are recommended, manufacturers begin to grow virus strains in fertile chicken eggs. The parent strains of vaccine, used by each manufacturer are tested by FDA to assure they are the same as the recommended strains;
- Review extensive manufacturing and clinical information, and conduct several inspections of the manufacturing facilities of additional sponsors of influenza vaccine INDs. These steps are designed both to improve shortage response capabilities and,

most important, to expand future manufacturing capacity for influenza vaccine in coming years by encouraging interest in and progress toward US licensure;

- Work closely with the UK regulatory authority (MHRA) to facilitate Chiron's remediation of its manufacturing problems at the Liverpool facility. These efforts involve frequent teleconferences, multiple site visits/inspections, and review of manufacturing and facility information. FDA is also interacting closely and proactively with the two other currently licensed influenza vaccine manufacturers, Aventis Pasteur and MedImmune on a variety of issues related to their vaccine manufacturing;
- Expedite lot release of influenza vaccine through the manufacturing time period. The process of manufacturing these vaccines is very complex, and is complicated by the large number of doses administered in a very short time frame; and,
- Work with manufacturers throughout the year to collect information on the capability of new influenza viruses to be used for large-scale production.

Combating Influenza

- *The influenza epidemic of 1918-1919 caused an estimated 20 million deaths worldwide, with little progress, until the 1930's.*
- *Today's flu vaccines are typically 70 to 90 percent effective in reducing a person's chances of getting the flu, but new strains are found annually.*
- *Every year CBER's Vaccines and Related Biological Products Advisory Committee meets to make recommendations for the strains to be used in making vaccines potentially saving millions of lives worldwide.*
- *CBER scientists perform vital serologic testing to determine whether current vaccines produce antibodies that inhibit the new influenza viruses and prevent a pandemic.*

Blood Safety

The blood supply is critical to the nation's health care system, and is the world's safest supply of blood. FDA's goal is to continue to help ensure the safety of the supply by minimizing the risk of infectious disease transmission and other hazards, while facilitating an adequate supply of whole blood and blood products; which is a critical underpinning of our health care system and of our emergency preparedness. FDA continues to strengthen efforts to protect the blood supply, and to minimize any risk to patients of acquiring HIV, hepatitis, Creutzfeldt-Jakob Disease (CJD), West Nile Virus (WNV) and other emerging blood-borne diseases, including potential agents of bioterrorism. These efforts include:

- Promulgating and enforcing standards for blood collection and for the manufacturing of blood products, including transfusable components of whole blood, pharmaceuticals derived from blood cells or plasma, as well as related medical devices and screening tests. FDA also inspects blood establishments; monitors reports

of product deviations and adverse clinical events; and, works closely with other parts of the PHS to establish blood standards, and to identify and respond to potential threats to blood safety or supply;

- Facilitating the development and review of innovative products to improve blood safety and availability such as new immunoglobulin and clotting factors, new methods to preserve blood cells and related products, artificial blood substitutes, new blood testing and safety technologies, as well as improved HIV tests for blood and for public health screening;
- Continuing to update existing guidance consistent with new scientific information and eliminate guidance documents lacking enforceability;
- Continuing to address emerging infectious diseases, ensuring compliance of plasma fractionation establishments, blood donor/recipient notification and look back, and FDA emergency and Class I recalls affecting blood safety response procedures;
- Responding to emerging potential threats to the blood supply, such as WNV, SARS, HIV variants; new hepatitis agents; human herpes virus-type 8; and CJD, in a timely and coordinated approach. In collaboration with the CDC and NIH, FDA engages in scientific investigations of emerging infectious agents. Actions include an assessment of the risk to the blood supply, diagnostic methods, standards development and regulatory controls; and,
- Continuing to emphasize the need to protect the nation's blood supply, and minimizing any risk of acquiring the human form of BSE, CJD, and other blood-borne diseases. No rapid diagnosis test of either BSE or CJD or for detection of infected tissue have been validated as either sufficiently specific or sensitive to be used to screen the blood supply. A reliable blood-screening test for CJD is an extremely important goal and is currently the object of considerable activity.

First Oral Fluid Based Rapid HIV Test Kit

On March 26, 2004, FDA approved the use of oral fluid samples with a rapid HIV diagnostic test kit that provides screening results with over 99 percent accuracy in as little as 20 minutes. Until the approval of this test kit, all rapid HIV tests required the use of blood.

The original version of this rapid test – the OraQuick Rapid HIV-1/2 Antibody Test, manufactured by OraSure Technologies, Inc., Bethlehem, Pa. – was approved on November 7, 2002, for detection of antibody to HIV-1 in blood. On March 19, 2004, FDA approved the test for detection of HIV-2 (a variant of HIV that is prevalent in parts of Africa but rarely found in the U.S.) in blood. Approval of this rapid HIV test kit represents another significant new use for the test. As when used on blood, this test can quickly and reliably detect antibodies to HIV-1. It can also be stored at room temperature and requires no specialized equipment.

"Before the approval of this rapid test in November 2002, many people being tested for HIV in public clinics did not return for the results of standard tests," said Secretary Thompson. "Where the rapid test is available, those tested get their results within minutes. This oral test provides another important option for people who might be afraid of a blood test. It will improve care for these people and improve the public health as well."

Through enhanced testing and other improvements in blood safety, the risk of transmission of viruses such as HIV, and hepatitis B and C through blood transfusion has been dramatically reduced. The risks of HIV and of HCV have been reduced from 1/100 units in the 1980's to less than 1-in-a-million at present.

Xenotransplantation

FDA regulates xenotransplantation products and is actively involved in developing guidance and working with the PHS agencies on crosscutting. Although the potential benefits of xenotransplantation products are considerable, the use of live-animal materials raises concerns regarding the potential infection of recipients with both recognized and unrecognized infectious agents, and the possible subsequent transmission into the human population. Potential cross-species infection with persistent viruses, such as retroviruses, is of particular public health concern because they may be latent and lead to disease years after infection. Moreover, new or emerging infectious agents may not be readily identifiable with current techniques.

Postmarket Monitoring

FDA engages in activities to ensure the continued quality and safety of previously approved biologic products. Because these products are derived from living organisms, they do not have the same manufacturing consistency as pharmaceutical products derived from chemical combinations. FDA must engage in post-approval activities to develop and validate test methods and establish standards for biological products.

Imports, Import Monitoring and Foreign Inspections

The explosion in the number of imports combined with the security concerns raised by terrorism and counterfeiting incidents has increased the need to physically assess the status of imported products, including biologics, as part of the Agency's emerging import strategy. Base funding will enable FDA to improve the safety of imported and domestic biological products and tissues by increasing the surveillance of imported human tissues and imported biological products and coordinate domestic field investigational analytical compliance activities.

Prescription Drug User Fee Act (PDUFA)

The Program has met or exceeds most of its PDUFA performance goals in FY 1994 through 2003. The BT Act reauthorized the collection of user fees to enhance the review process of new human drugs and biological products, and established fees for applications, establishments, and approved products. These amendments are effective for a five-year period with certain technical improvements. Specifically, Congress directed FDA to strengthen and improve the review and monitoring of drug safety; consider greater interaction with sponsors during the review of drugs and biologics intended to treat serious and life-threatening diseases; and, develop principles for improving first-cycle reviews. Review performance monitoring is being done in terms of fiscal year cohorts. The FY 2006 cohort performance goals include:

- Complete review and action on 90 percent of standard original NDA/BLA submissions within 10 months; and complete review and action on 90 percent of priority original NDA/BLA submissions within six months of receipt;
- Complete review and action on 90 percent of standard efficacy supplements within 10 months; and complete review and action on 90 percent of priority efficacy supplements within six months of receipt;
- Complete review and action on 90 percent of manufacturing supplements within six months of receipt, and complete review and action on 90 percent of manufacturing supplements requiring prior approval within four months of receipt; and,
- Complete review and action on 90 percent of Class 1 resubmitted original applications within two months; and complete review and action on 90 percent of Class 2 resubmitted original applications within six months of receipt.

EMPOWERING CONSUMERS FOR BETTER HEALTH

FDA enables consumers to make smarter decisions by getting them better information to weigh the benefits and risks of FDA-regulated products.

Communications with Stakeholders and Consumers

FDA is committed to carrying out our mission and is in constant consultation with experts in science, medicine, and public health and in cooperation with healthcare providers, consumers, and industry. FDA is also, enhancing communication methods in order to mitigate the risks due to the lack of accurate and timely information to the public about a biologic product. In pursuit of this objective FDA:

- Collaborates with scientists to support regulatory decisions by assessing risks associated with regulated products; setting standards that minimize risk and testing products against those standards; improving the usefulness and precision of risk assessment methods; and developing methods to increase the accuracy of sample analysis and detection of biological substances;
- Provides information on research projects and scientific articles emphasizing the importance of our regulatory research as mission critical work underpinning regulatory decisions;
- Maintains the program to increase access to new guidance documents, safety information and the opportunity to discuss important issues with Agency experts at numerous trade associations, scientific, and community meetings; and,
- Maintain outreach with industry and provide training as required by FDAMA and the Small Business Regulatory Enforcement Fairness Act.

PATIENT AND CONSUMER PROTECTION

FDA seeks continuous improvements in patient and consumer safety by reducing risks associated with FDA-regulated products. FDA's work on medical errors and SARS are examples of effort in this area.

Medical Errors

The prevalence of avoidable health complications that involve the use of FDA-regulated products, presents a challenge for FDA, whose central public health role is to help ensure that vaccines, blood and blood products, human cells, tissues, and cellular and tissue-based products are safe and effective. FDA also ensures that quality standards are adhered to by the various biological product establishments by:

- Conducting product safety biomedical research in areas such as new cells used to produce drugs and biologics. Rapid advances in technology and the evolving HIV pandemic necessitate the need to use new types of cell substrates and to develop new assays and assess the reliability of current assays used to monitor product safety. This is coupled with other international public health crises, such as hepatitis B/C infections, the constant threat of pandemic influenza, and the treatment of genetic defects;

- Developing new, specific and sensitive techniques and assays to validate and detect a greater variety of known potentially infectious viruses. A prime objective of safe biological products is detection, identification, and elimination of adventitious agents, which are agents that are infectious for humans. A chief concern inherent in biologicals is the potential for the presence of adventitious agents in the approved product;
- Enhancing the vaccines and biologics safety surveillance through ongoing programs for safety surveillance of cutting edge technology and its appropriate implementation;
- Maintaining the system of post-marketing surveillance and risk assessment program to identify adverse events that did not appear during the product development process by collecting, evaluating and acting on information of Adverse Event Reports (AERS) associated with marketed products;
- Maintaining reporting systems to collect biological product deviation events that occur during manufacturing processes or storage of biological products, including blood product manufacturers and blood-banking facilities; and,
- Establishing contracts for safety monitoring data links that include data on product exposure and extensive patient information. Develop access to external databases with other government agencies, states, academia and independent health organizations such as hospitals, to enhance FDA's ability to monitor the public health impact of FDA-regulated products.

Severe Acute Respiratory Syndrome (SARS)

The CDC and the WHO are investigating a worldwide outbreak of unexplained atypical pneumonia referred to as SARS. FDA is working with other government agencies, industry and academia to:

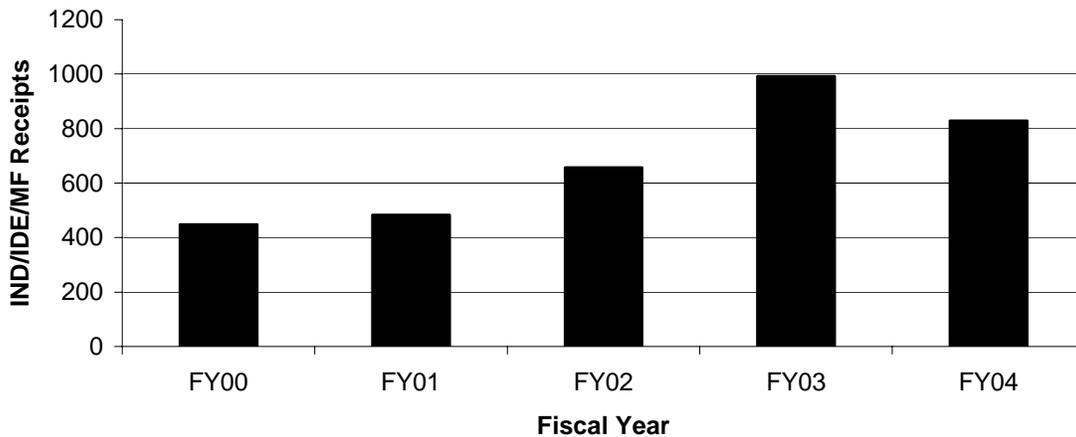
- Facilitate the development of reliable diagnostic tools, and safe and effective treatments for patients suffering from SARS, including a SARS vaccine;
- Assure that adequate supplies of various medical products are available in the event of the broader spread of SARS in the U. S.; and,
- Safeguard the blood supply against the potential threat of SARS.

FDA is pursuing multiple potential vaccine development strategies and is working with other government agencies and the private sector to address many of the most difficult issues in early vaccine development. In this process, guidance is provided on the use of animal test data and on safe manufacturing practices. FDA will also be a major participant in the design of clinical trials and in defining the needs of special populations, such as pregnant women. As the SARS vaccine program is in its infancy, much painstaking work is necessary to assure that the development and manufacturing processes meet the standards required to develop and produce safe and effective vaccines.

PROTECTING THE HOMELAND – COUNTERTERRORISM

The Agency’s strategic goal to “Protect America from Terrorism” focuses on preparation and response to a terrorist attack on the U.S. population. This includes the ability to facilitate the development and availability of medical countermeasures to limit the effects of a terrorist attack on the civilian or military populations.

CBER COUNTERTERRORISM IND/IDE RECEIPTS *



* The total number of counterterrorism IND/IDE/MF original submissions and amendments received during each fiscal year.

FDA plays a crucial role in protecting the public health by ensuring the availability of safe and effective medical countermeasures for mitigating the public health consequences of a bioterror event. The Program is responsible for regulating the development and licensure of new biological products including vaccines, blood products, human tissues, cells and gene therapies. Working closely with industry and government agencies, FDA works to help assure an adequate supply of these products which include products for immunization against anthrax, smallpox and other biothreats that might be used by terrorists as well as products to treat burn, blast and trauma injuries. FDA collaborates closely with other federal agencies to develop protocols, conduct animal studies, and define reference databases on treatment and alternative therapies for infectious diseases caused by the intentional use of biological agents. Applicable tests include those for bacterial and fungal sterility, general safety, purity, identity, suitability of constituent materials, and potency. Adverse events are monitored to identify patterns of significant reactions to these new vaccines. Support has been increased for the protection of regulated products from contamination and tampering to ensure availability of products. FDA works to:

- Ensure the safety and efficacy of biological products, including vaccines, blood and blood products, and diagnostic countermeasures to support the development, maintenance and deployment of stockpiles of medical countermeasures;

- Help ensure that sufficient quantities of medical products are available; and implement post-event follow-up and data collection for these products, some of which are investigational;
- Conduct and support active applied research programs directed towards optimizing the availability of safe and effective new products for the treatment, prevention or cure of diseases in humans;
- Evaluate the types of non-clinical data that may be acceptable for product licensure if pre-licensure clinical studies are not feasible or ethical;
- Evaluate over 100 active investigational new drug applications on products under development for use either to mitigate or prevent the pathological effects of terrorism-related pathogens in humans;
- Participate in activities to facilitate the availability of the currently approved vaccine for anthrax; and continue counterterrorism activities associated with the development of new smallpox and anthrax vaccines; vaccines for plague, tularemia, and Venezuelan Equine Encephalitis, as well as other encephalitis-causing viruses; and,
- Monitor production of biologics from the early stages all the way through post marketing with lot release testing to ensure the individual lots continue to meet safety, purity, potency and efficacy requirements.

IMPROVING FDA'S BUSINESS PRACTICES

The Agency strategic goal, "Improving FDA's Business Practices", focuses on the critical infrastructure that provides scientific support and administration to FDA's programs. This will ensure a world-class professional workforce, effective and efficient operations, and adequate resources to accomplish the Agency's mission. The managerial and operational efficiencies being pursued under this goal are aligned with the President's Management Agenda, the Secretary's priority of strengthening management by creating a more streamlined, cost-effective, and accountable organization, and the DHHS strategic goal to achieve excellence in management practices.

SELECTED FY 2004 ACCOMPLISHMENTS

USING RISK-BASED MANAGEMENT PRACTICES

In alignment with the Critical Path Initiative, CBER employs science-based approaches to solve current problems and anticipate future barriers to biologics product development and licensure. CBER strives to identify and work collaboratively to develop the scientific knowledge and tools to determine the safety and efficacy of products.

On October 7, 2004, a public workshop was held, entitled, “From Concept to Consumer: Center for Biologics Evaluation and Research Working with Stakeholders on Scientific Opportunities for Facilitating the Development of Vaccines, Blood and Blood Products, and Cellular, Tissue, and Gene Therapies.” It provided stakeholders a forum for discussing opportunities for and potential approaches to the development of innovative scientific knowledge and tools to facilitate the development and availability of new biological products.

Expanded Manufacturing Capacity for Prevnar

On April 16, 2004, CBER approved Wyeth Pharmaceuticals Inc.’s supplement to Wyeth’s biologics license application (BLA) for Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (Prevnar) to allow for filling and testing by a contract manufacturer, Cardinal Health Sterile Technologies. This approval aided in alleviating the shortage of Prevnar by expanding manufacturing capacity.

Cell and Gene Therapy: Outreach and Partnerships

CBER has provided proactive scientific and regulatory guidance in areas of novel product development. Openly communicating regulatory expectations and encouraging dialogue on points of cutting edge product development helps define the best scientific approaches and reduces product development time and risk. Focusing on how to best evaluate the most important issues in safety and efficacy helps avoid unnecessary regulatory burdens. In addition, engaging and supporting broad public interactions helps FDA and product developers to better address difficult issues involving risks and benefits of novel products. Examples during the past year include:

- Biological Response Modifiers Advisory Committee (BRMAC) – March 2004 meeting on issues related to the design of early phase clinical trials of cellular therapies for the treatment of cardiac diseases. Three important issues confronting the development of cellular products for the treatment of heart disease include manufacturing, catheter-cellular product interactions, and the nature and quantity of pre-clinical data needed to begin early phase clinical studies;
- BRMAC – October 2003 meeting on issues related to the type and quality of manufacturing, and preclinical and clinical data to be provided in a BLA for marketing approval of allogeneic islets as a treatment for type 1 diabetes mellitus;
- Stem Cell Clonality and Genotoxicity Retreat – December 2003 meeting that provided updates on preclinical models and an international perspective on clinical trials for Severe Combined Immunodeficiency Disease; and,
- CBER co-sponsored a workshop in June 2004, prior to the annual American Society of Gene Therapy meeting, that provided a forum for input from the community on the scientific, clinical, legal, social, and ethical issues surrounding conformance with long-term follow-up in gene transfer subjects.

Prescription Drug User Fee Act (PDUFA)

PDUFA established performance goals for the evaluation of applications for marketing drug and certain biological products. Review performance monitoring is being done in terms of cohorts, *e.g.*, the FY 2004 cohort includes applications received from October 1, 2003 through September 30, 2004.

Accomplishment of the cohort-year performance goals is not immediately measurable at the close of the fiscal year. The outcome can be measured after the last submission received in the fiscal/cohort year is acted upon, depending upon the category of submission.

Program has met or exceeded most of its performance goals from their inception in FY 1994 through FY 2003. The FY 2004 cohort review performance goals include:

- Complete review and action on 90 percent of standard original NDA/BLA submissions within 10 months; and complete review and action on 90 percent of priority original NDA/BLA submissions within six months of receipt;
- Complete review and action on 90 percent of standard efficacy supplements within 10 months; and complete review and action on 90 percent of priority efficacy supplements within six months of receipt;
- Complete review and action on 90 percent of manufacturing supplements within six months of receipt, and complete review and action on 90 percent of manufacturing supplements requiring prior approval within four months of receipt; and,
- Complete review and action on 90 percent of Class 1 resubmitted original applications within two months; and complete review and action on 90 percent of Class 2 resubmitted original applications within six months of receipt.

Medical Device User Fee and Modernization Act (MDUFMA)

MDUFMA provides the Biologics Program important new responsibilities, resources, and challenges. In exchange for user fees, FDA pursues a challenging and comprehensive set of device review performance goals that will significantly improve the timeliness, quality, and predictability of FDA's review of new devices. These goals were developed collaboratively by FDA, stakeholders, and Congressional staff.

Through its implemented changes, the Program has demonstrated that it has the ability to provide timely review of device submissions, consistent with the MDUFMA goals. Additionally, the Program has shown improved performance in review and approval of HIV-related diagnostic tests. However, it must be noted that, without the additive resources provided by the MDUFMA program, these results would not have been possible.

Blood Safety

On August 31 and September 1, 2004, CBER held a workshop on plasma standards, to aid in the development of standards for plasma that would address the regulatory concerns encountered over the years with the preparation, shipment, and use of plasma both for transfusion and in the manufacturing of blood products such as factor VIII and Immunoglobulin intravenous. Another major objective of the workshop was to gather information on current industry practices that are in place for the manufacturing of plasma including information on:

- Appropriate freezing and storage temperatures for the components;
- Appropriate time frame to freezing;
- Impact of time to freezing on final product;
- Identification of the recovered plasma component;
- Identifying date expiration for recovered plasma;
- Distinguishing recovered plasma from source plasma.

Tissue Action Plan

FDA has made significant progress towards completing the tissue action plan deliverables. FDA published the third of three proposed rules on November 18, 2004, intended to implement the tissue action plan. This rule requires establishments that recover, process, store, label, package, or distribute tissue, or that screen or test donors, to follow current good tissue practice requirements. The proposed rule also contains provisions for FDA inspection of establishments and enforcement of the regulations. FDA had already published final rules requiring human cell, tissue, and cellular and tissue-based product (HCT/P) establishments to register and list with the Agency as well as to perform donor screening.

PATIENT AND CONSUMER PROTECTION

West Nile Virus

West Nile Virus, first found in Africa in 1937, was identified in the Western Hemisphere for the first time in 1999 in the New York City area. Since then, it has spread quickly throughout most of the U. S. From January 2003 to the end of October 2003, 44 states and the District of Columbia reported more than 7,700 human cases of WNV infection, resulting in 166 deaths.

CBER and CDC have proven that WNV is transmitted by blood transfusion as well as tissue transplants. It is difficult to detect WNV due to low levels of virus in the blood and tissues. Though it is not possible to predict the incidence or severity of future WNV epidemics, the evidence suggests that all or most of the U.S. would be at risk for exposure to this illness each year.

CBER meets regularly with blood banks, CDC, and NIH to coordinate epidemiology and monitor test results, such as the December meeting of the Blood Products Advisory Committee in Gaithersburg, Maryland. The committee was updated on the WNV

epidemic and donor testing in 2003, including updates on WNV testing under investigational new drug applications and plans for 2004.

Xenotransplantation Action Plan

The development of xenotransplantation is, in part, driven by the fact that the demand for human organs for clinical transplantation far exceeds the supply. During 2002, more than 15 U.S. patients died while awaiting life-saving vital organ transplants. Moreover, recent evidence has suggested that transplantation of cells and tissues may be therapeutic for certain diseases such as neurodegenerative disorders and diabetes, where, again, human materials are not usually available. Although the potential benefits are considerable, the use of xenotransplantation raises concerns regarding the potential infection of recipients with both recognized and unrecognized infectious agents and the possible subsequent transmission to their close contacts and into the general human population. Of public health concern is the potential for cross-species infection with retroviruses, which may be latent and lead to disease years after infection. Moreover, new infectious agents may not be readily identifiable with current techniques.

Highlights of significant regulatory and policy accomplishments in FY 2004 are:

- The Xenotransplantation Product IND Reviewer Focus Group, consisting of the cross-disciplinary staff responsible for the review of xenotransplantation submissions. The Group meets regularly to discuss: application of the principles set forth in relevant FDA regulations; current scientific and medical data and literature relevant to transplantation; current status of xenotransplantation applications submitted to the Agency, and the unique issues that these products may present; and to highlight areas of concern where further expert advice may be needed;
- CBER reviewers continue to meet with and advise sponsors of ongoing and future clinical trials in xenotransplantation, and to work with other FDA Centers to ensure consistent regulation of xenotransplantation across FDA;
- The Secretary's Advisory Committee on Xenotransplantation met on February 24, 2004 to discuss two draft reports that addressed the state of the science as well as informed consent issues in xenotransplantation. Additional presentations and discussion focused on recent advances in xenotransplantation research, including a report of a clinical study of porcine islet xenotransplantation in type 1 diabetic patients, and results from recent studies of porcine endogenous retrovirus; and
- Continued CBER involvement in international activities for the safety and regulation of xenotransplantation products was instrumental in a WHO resolution approved by the World Health Assembly on May 22, 2004. The resolution calls for xenotransplantation to occur only in countries with appropriate oversight, international cooperation for development of guidelines, and collaboration and coordination for prevention and surveillance of xenotransplantation-derived infections.

New Requirements for E-Labeling of Biologics Applications

On December 9, 2003, FDA amended regulations to require electronic submission of labeling for review with certain BLA's, supplements and annual reports. This new rule is another step in FDA's efforts to use modern information technology to help inform the public and improve patient safety.

Sponsors are now required to submit to FDA in electronic format the content of the package insert or professional labeling, including all text, tables and figures. Electronic labeling of information will improve the labeling review process and speed up the approval and public dissemination of labeling changes, getting important, up-to-date information on medications to doctors and patients more quickly. Labeling content must be submitted in a form described in Agency guidance on electronic submissions. This standard format will allow FDA to process, review, archive, and distribute the information publicly.

New Requirements for Bar Codes on Drugs and Blood

On February 25, 2004, Secretary Thompson announced the FDA was issuing a final rule requiring bar codes on the labels of thousands of human drugs and biological products. The measure helps protect patients from preventable medication errors, reduces the cost of health care, and represents a major step forward in the Department's efforts to harness information technology to promote higher quality care.

"Bar codes help doctors, nurses, and hospitals make sure that they give their patients the right drugs at the appropriate dosage," Secretary Thompson said. "By giving health-care providers a way to check medications and dosages quickly, we create an opportunity to reduce the risks of medication errors that can seriously harm patients."

FDA first proposed bar-code requirements in March 2003 and received comments from hospitals, health care professionals, trade and professional associations and others showing widespread support for the approach. FDA estimates that the bar-code rule, when fully implemented, will help prevent nearly 500,000 adverse events and transfusion errors over a period of 20 years. The economic benefit of reducing health care costs, reducing patient pain and suffering, and reducing lost work time due to adverse events is estimated to be \$93 billion over the same period.

The final rule applies to most drug manufacturers, repackers, relabelers, private label distributors and blood establishments. New medications covered by the rule will have to include bar codes within 60 days of their approval; most previously approved medicines and all blood and blood products will have to comply with the new requirements within two years.

PROTECTING HOMELAND -- COUNTERTERRORISM

FDA plays a crucial role in protecting the public health by ensuring the availability of safe and effective medical countermeasures for mitigating the public health consequences

of a bioterror event. The Agency's responsibility is to regulate the development and licensure of new biological products, including vaccines, blood and blood products, human tissues and cells and gene therapies. FDA also collaborates closely with other federal agencies, such as DOD, NIH, and CDC to develop protocols, conduct animal studies, and define reference databases on treatment and alternative therapies for infectious diseases caused by the intentional use of biological agents. Major counterterrorism activities during FY 2004 included:

- October 23, 2003, approval of BabyBIG, Botulism Immune Globulin Intravenous (Human) (BIG-IV), California Department of Health Services, Berkeley, California. BabyBIG is indicated for treatment of infant botulism caused by type A or type B *Clostridium botulinum*;
- April 29, 2004, approval of supplement to the BLA for Anthrax Vaccine Adsorbed (BioThrax), manufactured by BioPort Corporation, Lansing, Michigan, to include an extension of dating to 24 months;
- Final rule and final order regarding the safety and efficacy of certain licensed biological products including anthrax vaccine, December 30, 2003. The final order states the conclusion that the licensed anthrax vaccine, Anthrax Vaccine Adsorbed, is safe and effective for the prevention of anthrax disease - regardless of the route of exposure;
- Direct final rule to allow for greater flexibility when manufacturing with spore-forming microorganisms in the production of vaccines and counter-terrorism products [21 CFR 600.11(e) (4)]. This rule went into effect June 1, 2004, and the accompanying guidance document is in the final stages of clearance before publishing for comment; and
- Workshop on October 23 – 24, 2003, "Counter Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development."

IMPROVING FDA'S BUSINESS PRACTICES

Electronic Document Room (EDR)

This collection of systems receives electronic transmission of information from industry and FDA. The EDR stores, retrieves, and distributes electronic submissions to reviewers, and is integrated with regulatory databases to allow for advanced searches based on data in CBER databases. The EDR automates processing of submissions and automatically sends notifications to reviewers, and serves as a repository for generated final documents.

Gene Therapy Patient Tracking System Development (GTPTS)

This integrated system for the collection and analysis of information to assess and promote gene therapy product safety. The GTPTS represents a comprehensive evaluation and re-engineering of FDA approaches regarding data pertinent to the safety of recipients of gene therapies, including collection of data from gene therapy recipients; and use of the data and analyses to make informed regulatory decisions and increase the understanding of researchers, subjects, and the public.

Genetic Modification Clinical Research Information System (GeMCRIS)

On March 26, 2004, FDA and NIH announced a new GeMCRIS – a web-accessible database on human gene transfer. This collaboratively developed system is a unique public information resource as well as an important new electronic tool to facilitate the reporting and analysis of adverse events in clinical trials. The new system will provide information directly to the public and will improve the government’s ability to monitor adverse events in gene transfer research, also known as gene therapy.

Acting Commissioner, Crawford, emphasized that “the development of GeMCRIS illustrates the government’s commitment to addressing public and patient concerns about safety while advancing gene therapy. Providing accurate and complete information about ongoing gene therapy studies is the best way to achieve this goal.”

GeMCRIS will enable patients, research participants, scientists, sponsors, and the public at large to become better informed about gene transfer research. Through drop-down menus and preformatted reports, individuals can easily navigate the GeMCRIS site to view information on particular characteristics of clinical gene transfer trials. For example, GeMCRIS users can learn where trials are taking place, which diseases or health conditions are being studied, and what investigational approaches are being taken. While offering a rich array of information of value to many types of users, GeMCRIS also includes special security features to protect patient privacy and confidential commercial information.

Creation of Tissue Safety Teams

CBER has improved monitoring of tissue safety by implementing the interdisciplinary and cross-office teams to monitor and analyze adverse event reports and, as an ultimate goal, move toward a system of active surveillance. This includes the development of Standard Operating Procedures to facilitate reporting and specify procedures for the receipt and investigation of adverse events. This will involve coordination of training, outreach, inspection, and compliance activities.

**Biologics
Program Activity Data**

PROGRAM WORKLOAD AND OUTPUTS	FY 2004 Actuals	FY 2005 Estimate	FY 2006 Estimate
Total Original License Application (BLA) Reviews ^{1/}	11	15	18
BLA Approvals	7	10	10
Median BLA Approval Time (months)	16.53	12.0	14.0
License Supplement (BLA) Reviews ^{1/}	2,496	2,500	2,500
NDA & NDA Supplement Approvals	69	70	70
ANDA & ANDA Supplement Approvals	2	3	3
PMA & PMA Supplement Reviews ^{1/}	29	30	30
510(k) Reviews ^{1/}	100	100	100
Commercial IND/IDE Receipts	132	140	150
IND/IDE Amendments Receipts ^{2/}	7,884	8,300	8,700
Active INDs/IDEs ^{2/}	2,626	2,700	2,750
Adverse Event Report Receipts ^{3/}	20,400	21,000	21,000
Biological Product Deviation Reports Receipts	38,164	40,000	40,000

1/Total of approval, and complete decisions. Does not include refuse-to-file decisions or withdrawals.

2/Includes IND, IDE, Master File and license master file receipts.

3/Includes MedWatch, Foreign reports and VAERs reports. Does not include Fatality Reports or Medical Device Reports for CBER-regulated medical devices.

PERFORMANCE GOALS AND TARGETS

The following table of performance goals and FY 2006 targets is presented to compliment the sequential display of this program's "outputs" by more closely linking the traditional budget presentation of base and increased activities and workload outputs contained in the Program Activity Data (PAD) charts. Activities discussed throughout this narrative support the accomplishment of outputs (PAD and performance goals) which in turn contribute to the accomplishment of long term outcome and strategic goals. Full cost information for these goals as well as other historical information has been provided in their respective sections in the Detail of Performance Analysis contained in the supporting information tab.

Performance Goals	Targets
Complete review and action on 90% of standard original PDUFA NDA/BLA submissions within 10 months; and review and act on 90% of priority original PDUFA NDA/BLA submissions within 6 months of receipt. (13001)	FY 06: Standard Applications within 10 months: 90% Priority Applications within 6 months: 90%
Complete review and action on 90% of standard PDUFA efficacy supplements within 10 months; and review and act on 90% of priority PDUFA efficacy supplements within 6 months of receipt. (13002)	FY 06: Standard Applications within 10 months: 90% Priority Applications within 6 months: 90%
Complete review and action on 90% of complete blood bank and source plasma BLA submissions and 90% of BLA supplements within 12 months after submission date. (13005)	FY 06 : BLA Submissions: 90% BLA Supplements 90%