

**HUMAN DRUGS  
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)**

|                                    | <b>FY 2004<br/>Actual</b> | <b>FY 2005<br/>Enacted <sup>1/</sup></b> | <b>FY 2006<br/>Estimate</b> | <b>Increase<br/>or Decrease</b> |
|------------------------------------|---------------------------|--|-----------------------------|---------------------------------|
| <b>Program Level</b>               | <b>\$396,491,000</b>      | <b>\$439,284,000</b>                     | <b>\$456,933,000</b>        | <b>+\$17,649,000</b>            |
| <i>Total FTE</i>                   | <i>2,190</i>              | <i>2,395</i>                             | <i>2,412</i>                | <i>+17</i>                      |
| <b>Budget Authority</b>            | <b>\$229,372,000</b>      | <b>\$230,588,000</b>                     | <b>\$233,881,000</b>        | <b>+\$3,293,000</b>             |
| <i>Office of Drug Safety</i>       | <i>\$15,800,000</i>       | <i>\$17,900,000</i>                      | <i>\$22,900,000</i>         | <i>+\$5,000,000</i>             |
| <i>GSA Rent and Rent Related</i>   | <i>\$18,544,000</i>       | <i>\$20,059,000</i>                      | <i>\$20,518,000</i>         | <i>+\$459,000</i>               |
| <i>Administrative Efficiencies</i> | <i>N/A</i>                | <i>N/A</i>                               | <i>\$301,000</i>            | <i>-\$301,000</i>               |
| <i>IT Reduction</i>                | <i>N/A</i>                | <i>N/A</i>                               | <i>\$1,865,000</i>          | <i>-\$1,865,000</i>             |
| <i>Total FTE</i>                   | <i>1,218</i>              | <i>1,380</i>                             | <i>1,380</i>                | <i>0</i>                        |
| <b>User Fee</b>                    | <b>\$167,119,000</b>      | <b>\$208,696,000</b>                     | <b>\$223,052,000</b>        | <b>+\$14,356,000</b>            |
| <i>PDUFA</i>                       | <i>\$167,119,000</i>      | <i>\$208,696,000</i>                     | <i>\$223,052,000</i>        | <i>+\$14,356,000</i>            |
| <i>FTE</i>                         | <i>972</i>                | <i>1,015</i>                             | <i>1,032</i>                | <i>+17</i>                      |

|                         |                     |                     |                     |                   |
|-------------------------|---------------------|---------------------|---------------------|-------------------|
| <b>ORA Estimate</b>     | <b>\$98,346,000</b> | <b>\$97,960,000</b> | <b>\$98,972,000</b> | <b>+1,012,000</b> |
| <i>Budget Authority</i> | <i>\$93,525,000</i> | <i>\$92,654,000</i> | <i>\$92,770,000</i> | <i>\$116,000</i>  |
| <i>FTE</i>              | <i>725</i>          | <i>670</i>          | <i>635</i>          | <i>-35</i>        |
| <i>User Fee</i>         | <i>\$4,821,000</i>  | <i>\$5,306,000</i>  | <i>\$6,202,000</i>  | <i>+\$896,000</i> |
| <i>FTE</i>              | <i>34</i>           | <i>28</i>           | <i>29</i>           | <i>+1</i>         |

*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.*

<sup>1/</sup>*Contains budget authority rescission of 0.8 percent.*

**Historical Funding and FTE Levels**

| <b>Fiscal Year</b>        | <b>Program Level</b> | <b>Budget Authority</b> | <b>User Fees</b> | <b>Program Level<br/>FTE</b> |
|---------------------------|----------------------|-------------------------|------------------|------------------------------|
| 2002 Actual <sup>1/</sup> | \$273,008,000        | \$178,017,000           | \$104,093,000    | 1,834                        |
| 2003 Actual               | \$313,940,000        | \$188,837,000           | \$125,103,000    | 1,901                        |
| 2004 Actual <sup>2/</sup> | \$396,491,000        | \$229,372,000           | \$167,119,000    | 2,190                        |
| 2005 Enacted              | \$439,284,000        | \$230,588,000           | \$208,696,000    | 2,395                        |
| 2006 Estimate             | \$456,933,000        | \$233,881,000           | \$223,052,000    | 2,412                        |

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

<sup>1/</sup>*Includes FDA's FY 2002 Appropriation and the Counterterrorism Supplemental.*

<sup>2/</sup>*Includes the transfer of CBER's Therapeutics program.*

## STATEMENT OF BUDGET REQUEST

CDER is requesting \$456,933,000 in program level resources for accomplishing its mission activities including:

- Ensuring that prescription, generic, and Over-the-Counter (OTC) drug products are adequately available to the public and are safe and effective;
- Monitoring the use of marketed drug products for unexpected health risks; and,
- Monitoring and enforcing the quality of marketed drug products.

### PROGRAM DESCRIPTION

Within the human drug program, CDER is responsible for ensuring that America's drug product supply is adequately available, safe and effective, and of the highest quality. The process for approving drug products begins with the drug companies who must first test their products. CDER monitors their clinical research to ensure that people who volunteer for studies are protected and that the quality and integrity of scientific data are maintained, and assembles a team of physicians, statisticians, chemists, pharmacologists, and other scientists to review the company's data and proposed use of the drug. If the drug is effective and we are convinced its health benefits outweigh its risks, we approve it for sale. CDER does not actually test the drug when we review the company's data. By setting clear standards for the evidence FDA needs to approve a drug, the Agency helps medical researchers bring new drugs to American consumers more rapidly. CDER also reviews over-the-counter and prescription drugs and generic versions of these drugs.

Once a drug is approved for sale in the U.S., FDA's consumer protection mission continues. FDA monitors the use of marketed drugs for unexpected health risks. If new, unanticipated risks are detected after approval, we take steps to inform the public and change how a drug is used or even remove a drug from the market. We also monitor manufacturing changes to make sure they won't adversely affect the safety or efficacy of the medicine. CDER evaluates reports about suspected problems from manufacturers, health care professionals, and consumers. Sometimes, manufacturers run into production problems that might endanger the health of patients who depend on a drug. CDER tries to make sure that an adequate supply of drugs is always available.

ORA supports CDER by conducting preapproval inspections of both foreign and domestic establishments and other premarket-related activities such as: bioresearch monitoring of clinical research and laboratory method validations needed for premarket application decisions, and inspections of manufacturing facilities to determine if the factory is able to manufacture the product to the specifications stated in the application. The Field conducts risk-based domestic and foreign postmarket inspections of medical device manufacturers to assess their compliance with GMP requirements, and conducts inspections of reproducers of single-use devices, and monitors imported medical devices and radiological products through field examinations or sampling, as needed, to ensure the safety of such products.

In addition to overseeing regulated products on a surveillance or "for cause" basis when a problem is encountered, ORA staff also responds to emergencies and investigates

incidents of product tampering and terrorist events or natural disasters that may impact FDA regulated goods. 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 \$98,972,000 in support of the CDER Program.

Accurate and complete information are vital to the safe use of drugs. Drug companies have historically promoted their products directly to physicians, but increasingly are advertising directly to consumers. While the Federal Trade Commission regulates advertising of OTC drugs, we oversee the advertising of prescription drugs. Advertisements for a drug must contain a truthful summary of information about its effectiveness, side effects, and circumstances when its use should be avoided. We are monitoring the industry's voluntary program to provide consumers useful information about prescription drugs when they pick up their prescriptions. We are watching this program closely to see that it meets its goals for quantity and quality of information.

In addition to setting standards for safety and effectiveness testing, CDER also sets standards for drug quality and manufacturing processes, working closely with manufacturers to see where streamlining can cut red tape without compromising drug quality. As the pharmaceutical industry has become increasingly global, we are involved in international negotiations with other nations to harmonize standards for drug quality and the data needed to approve a new drug. This harmonization will go a long way toward reducing the number of redundant tests manufacturers do and help ensure drug quality for consumers at home and abroad.

FDA conducts and collaborates on focused laboratory research and testing. Research maintains and strengthens the scientific base of our regulatory policy-making and decision-making. The Agency focuses on drug quality, safety, and performance; improved technologies; new approaches to drug development and review; and regulatory standards and consistency.

## **CDER PERFORMANCE ANALYSIS**

During the latest performance period (FY 2004), CDER successfully met all nine of its performance goals. 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.

With the renewal of the Prescription Drug User Fee Act (PDUFA III) of 2003, CDER's targets for FY 2004 have reached full performance level. To sustain these ambitious targets, adequate funding is required. 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 original standard NDAs within 10 months of receipt and 90% of original priority NDAs within 6 months of receipt. | 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. | FDA's timely performance of high-quality drug reviews in recent years reflects the importance of managerial reforms and substantial additional resources provided under the Prescription Drug User Fee Act (PDUFA). |

## 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 and selected FY 2004 accomplishments 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 Animal Drugs and Feed 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 services 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**

### **Office of Drug Safety: +\$5,000,000 and +20 FTE**

CDER is responsible for ensuring that the U.S. drug supply is adequately available, safe and effective, and of the highest quality, these are mission-critical functions. Drug safety analysis and decision-making is the result of collaborative efforts among offices across the Center. CDER's Office of Drug Safety (ODS) is one such office involved in the overall drug safety function. The \$5,000,000 increase in funding will be used to strengthen the drug safety functions within ODS by: hiring additional staff to manage and lead safety reviews; increasing the number of staff with expertise in critical areas such as risk management, risk communication, and epidemiology; and, increasing access to a wide range of clinical, pharmacy and administrative databases.

### **GSA Rent: +\$459,000**

To help meet the rising costs of GSA rent, a total of \$4,100,000, of which \$459,000 is for the Center for Drug Evaluation and Research. This increase will cover inflation on FDA's current GSA leased facilities and the increased rental costs for the White Oak facility.

### **Management Savings: -\$2,166,000 and -9 FTE**

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

- **Administrative Efficiencies: - \$301,000 and – 3 FTE**  
Administrative efficiency savings will total -\$1,554,000 and -14 FTE, of which CDER's share is -\$301,000 and -3 FTE.
- **Information Technology Reduction: - \$1,865,000 and – 6 FTE**  
IT reductions will total -\$5,116,000 and -15 FTE, of which CDER's share is - \$1,865,000 and -3 FTE.

## **User Fee**

### **Prescription Drug User Fee Act III (PDUFA): + \$14,356,000 and + 17 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 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 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.

## JUSTIFICATION OF BASE

### USING RISK-BASED MANAGEMENT PRACTICES

The Human Drugs Program within FDA is responsible for ensuring the safety and effectiveness of drug and therapeutic biologic products. The following sections describe our responsibilities.

#### New Drug Review

FDA reviews and evaluates New Drug Applications (NDAs) to determine whether or not a new drug is both safe and effective. Drugs for diseases such as cancer and AIDS are given priority status and evaluated through an accelerated approval process. FDA's accelerated drug approval program helps make promising products for serious or life threatening diseases available earlier in the development process by allowing approval to be based on a

promising effect of the drug, such as tumor shrinkage, before there is actual evidence of improved survival or other clinical benefit. The drug's commercial sponsor worked closely with FDA to define the studies that would be conducted.

#### *Fast Track Approval for Erbitux*

*FDA approved Erbitux (cetuximab) to treat patients with advanced colorectal cancer that has spread to other parts of the body. Erbitux is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan.*

New Drug Application Review activities include:

- Regulating testing of Investigational New Drugs (INDs);
- Evaluating standard and priority NDAs received from sponsors; and,
- Completing review and action on standard and priority efficacy supplements – supplemental applications proposing to add a new use of an approved drug to a product's labeling.

### **Biological Therapeutic Products**

FDA reviews and evaluates biological therapeutic products, including establishing standards, conducting mission related research, participating in inspections, developing policy and procedures, and evaluating trial results and reports of adverse events. Biological therapeutic products include such products as growth factors, enzymes, monoclonal antibodies, and products prepared by genetic engineering and synthetic procedures. The human drug program monitors 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.

### **PDUFA**

The BT Act of 2002 reauthorized PDUFA for five years, allowing 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. Specifically, Congress directed FDA to strengthen and improve the review and monitoring of drug safety; consider greater interaction between the Agency and 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. Performance monitoring of reviews is accomplished in terms of cohorts. For example, the FY 2004 cohort includes applications received from October 1, 2003 through September 30, 2004. The FY 2005 cohort review performance goals covered under PDUFA for NDAs, Product License Applications (PLAs), and Biologics License Applications (BLAs) are:

- Review and act on 90 percent of standard original NDA and BLA submissions filed during the fiscal year within 10 months of receipt;
- Review and act on 90 percent of priority original NDA and BLA submissions filed during the fiscal year within 6 months of receipt;
- Review and act on 90 percent of standard efficacy supplements filed during the fiscal year within 10 months of receipt; and review and act on 90 percent of priority efficacy supplements filed during the fiscal year within 6 months of receipt;
- Review and act on 90 percent of manufacturing supplements filed during the fiscal year within 6 months of receipt; and review and act on 90 percent of manufacturing supplements requiring prior approval within 4 months of receipt; and,
- Review and act on 90 percent of Class 1 resubmitted original applications filed during the fiscal year within 2 months of receipt; and review and act on 90 percent of Class 2 resubmitted original applications filed during the fiscal year within 6 months of receipt.

### **Over-the-Counter Drugs**

FDA is committed to providing consumers with safe, effective, and affordable drugs. Increasing the number of safe and effective OTC drugs that are available to consumers is consistent with this goal. This Program reviews OTC drugs to ensure their safety and effectiveness and assists consumers on how to best use OTC products by providing clear,

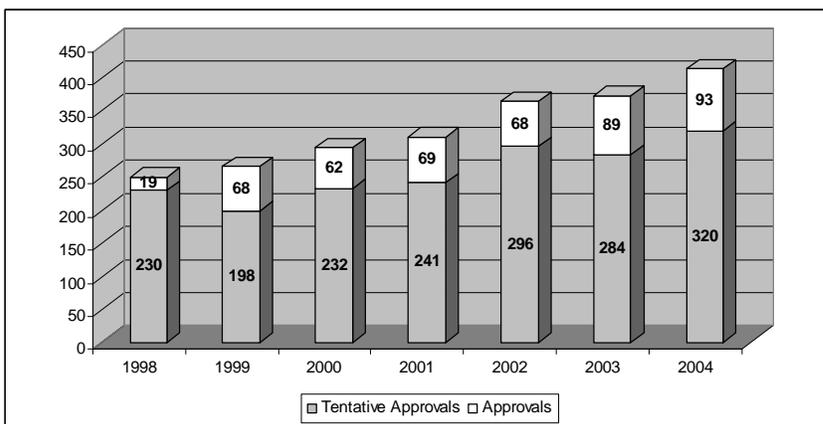
easy-to-read drug information. This program also enters into contracts for consumer behavior research to identify and manage risks associated with the use of OTC drugs.

OTC Drug Review was implemented to determine which OTC drugs could be recognized by experts as safe and effective for their intended uses. This was accomplished by using a system of monographs that serve as regulations covering the acceptable active ingredients and labeling for each category of OTC drug covered by the applicable monograph. OTC drugs that meet the requirements of the controlling monograph do not require approval through the NDA process and are not deemed to be misbranded. Those drugs that do not meet monograph requirements are considered new drugs requiring approval and, absent that approval, are misbranded.

### **Generic Drugs**

FDA continues to support an active generic drugs program to complete review and action on Abbreviated New Drug Applications (ANDAs), with a continued focus on expanding the availability of high-quality generic drug products and providing consumers with information on their safety and effectiveness. Generic drugs save consumers billions of dollars each year. Accordingly, FDA is committed to bringing as many safe and effective generic drugs to market as possible by addressing specific scientific questions regarding bioequivalence and chemistry of generic products. This research will be directed at evaluating ways to enable approval of generic drugs in areas that currently lack generic alternatives, such as inhalation or topical drug products. We are responsible for assuring generic product conformance to manufacturing standards equal to the standards of the brand name pharmaceuticals.

Further, FDA is working to increase efficiency and improve generic drug review times by evaluating ways to improve communications with industry. We have developed procedures to call the applicant during the review for clarification or explanation in order for the reviewer to continue and finalize an initial review. In



the late stages of review, the reviewer may communicate deficiencies that can be resolved easily, usually within 10 working days. Also, if there are multiple review cycles, the review staff attempts to discuss deficiencies with the applicant to ensure that the applicants understand what is being asked. In addition, FDA's Office of Generic Drugs (OGD) is participating in workshops and meetings with the industry to provide information to promote more complete, efficiently reviewed applications.

In addition, FDA will continue its efforts to enhance OGD information technology capabilities to further refine and develop electronic submissions of generic drug

applications to gain efficiencies in the review process and to train staff on the use, development, and expansion of electronic review efforts.

### **FDA Involvement in the President's Emergency Plan for AIDS Relief**

In the 2003 State of the Union address, President Bush announced his five-year, \$15 billion plan for emergency relief to nations in Africa and the Caribbean whose populations are most afflicted with HIV/AIDS. In May 2004, in direct support of the President's Emergency Plan for AIDS Relief (PEPFAR), Secretary Thompson announced that FDA would implement a new, expedited review process to ensure that the US could provide safe, effective drugs to developing countries. FDA plays a significant role in the PEPFAR initiative by providing the medical and scientific expertise necessary to fulfill the President's commitment to ensure the quality of HIV/AIDS drugs purchased by the US for developing countries. FDA's responsibilities include performing outreach to pharmaceutical firms – including many foreign firms who are unfamiliar with FDA's regulatory processes. FDA will conduct its traditional drug product review activities for both new products and for generic forms of existing drug products to ensure product safety and effectiveness. Given many firms will have little or no experience with FDA, the Agency will not have existing information about most clinical laboratories and manufacturing sites associated new drug and generic drug products seeking approval within the PEPFAR initiative. Therefore, FDA will conduct pre-approval inspections of laboratories and current good manufacturing practices (cGMP) inspections to ensure drug product quality during manufacturing. After approval, FDA will monitor the drug products by reviewing adverse event reports to ensure continued post market safety and will review any changes made to approved products to ensure that they are still safe and effective. FDA has estimated costs for support of the PEPFAR Initiative based upon the assumption that additional funding will be available to FDA to address the added workload of PEPFAR because, in addition to PEPFAR-specific work, FDA is currently staffed to a level to handle our existing workload for meeting PDUFA deadline. Further, given that FDA will support PEPFAR activities with existing experienced and highly-skilled personnel, FDA is assuming that funding received for the PEPFAR initiative will be used to “backfill” positions with new hires to satisfy the on-going workload demands, specifically the demands of PDUFA.

### **Protecting America's Children**

Due to the inadequacy of pediatric use information found in the majority of prescription medications in the U.S., Congress enacted several legislative initiatives to promote drug development for children.

In 1997, as part of the FDA Modernization Act, Congress enacted a law to provide marketing incentives to manufacturers who conduct studies in children. This law, which provides six months exclusivity in return for conducting pediatric studies requested by the FDA, was reauthorized in January 2002 under the Best Pharmaceuticals for Children Act (BPCA).

As a result of these initiatives, the number of ongoing pediatric clinical trials in the last 5 years has increased dramatically. Many of the studies reported to date have yielded new

dosing and safety information in labeling. FDA will continue to use base resources for issuing written requests (WR) for on-patent drugs, reviewing the studies, negotiating labeling changes within the 6-month timeframe, make publicly available the summaries of the medical and clinical pharmacology reviews, and monitoring adverse events for those drugs granted pediatric exclusivity.

The BPCA also established a publicly funded contracting process for studies of drugs that no longer have exclusivity or patent protection for which pediatric studies are needed. This process parallels the resources need for on-patent drugs. Moreover, FDA is mandated to collaborate with NIH to transform WRs for off-patent drug into Requests for Proposals (RFPs) which require FDA resources to review and provide comment to proposals from offerors.

The Pediatric Research Equity Act (PREA), enacted December 3, 2003, provides FDA the authority to require pediatrics studies for certain new and already marketed drug and biological products. It incorporates many elements of the former "Pediatric Rule" (63 FR 66632, Dec. 2, 1998) that was struck down in U.S. District Court for the District of Columbia on October 17, 2002. The effective date of PREA is April 1, 1999, the same date the former Pediatric Rule became effective. Due to the retroactive nature of the legislation, a significant number of previously submitted applications are now subject to the requirements. It is anticipated this initiative will require substantial base resources for addressing applications previously submitted, negotiating pediatric drug development plans, reviewing and making determinations on requests for waiver or deferral of pediatric assessments, reviewing submitted pediatric studies, and tracking all the information regarding waivers, deferrals and completed for affected applications.

### **Product Quality**

Ensuring that the highest possible quality products are marketed is a large part of FDA's mission. This is done by facilitating effective and efficient scientific assessment of relevant pharmaceutical and biotechnology information in regulatory submissions. The Agency facilitates scientific and technological innovations that improve understanding of product performance, quality and efficiency of development, manufacturing, and quality assurance processes. FDA works to support the achievement of the following attributes of drug products:

- Drug quality and performance achieved and assured through design of effective and efficient development and manufacturing processes;
- Regulatory specifications based on a mechanistic understanding of how product and process factors impact product performance; and,
- Continuous "real time" assurance of quality.

Ensuring quality of products involves recognizing the level of scientific knowledge supporting product applications, process validation, and process capability. FDA applies risk-based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product performance and to the

capability of process control strategies to prevent or mitigate risk of poor product performance.

Within the human drugs program, FDA evaluates and analyzes inspection findings for trends in deficiencies by focusing on product quality standards and manufacturers' compliance with GMP regulations. The Agency develop, deploy, and maintain risk-based compliance inspection models for prioritizing GMP inspections by risks to product quality. The Agency performs targeted drug quality surveillance studies to detect emerging threats to drug quality and develop baselines for risk-based drug quality monitoring by creating data resources and maintaining access to industry data resources for efficient and accurate assessments of drug products marketed and drugs consumed.

The Agency conducts criminal investigations of reported product tampering, counterfeit products, and other fraudulent criminal activities involving regulated drug products. We perform laboratory validation of analytical methods submitted to support pre-market product applications. FDA verifies the reliability and accuracy of NDA data collected by regulated industry in animal and human studies, and we evaluate approaches that may be used to facilitate the introduction of modern process analytical technologies and pharmaceutical engineering principles.

#### **Managing Quality by Industry Self-Compliance**

FDA operates a comprehensive program to guide, assist, and manage industry self-compliance with manufacturing quality objectives of the FDCA Act. We organize FDA experience and expertise into published guidance on how Industry may meet requirements for manufacturing quality on focused areas of technology and procedures. We provide input on industry-generated voluntary standards and guidance documents to assure broad consensus for effective compliance.

Over the last few years, FDA has conducted a major effort to bring a 21<sup>st</sup> century focus to the regulation of pharmaceutical manufacturing and product quality by providing high quality, cost-effective oversight of industry manufacturing, processing and distribution. FDA focuses on product quality standards and compliance by manufacturers with the GMP regulations to ensure that the highest possible quality products are marketed. We ensure the latest technological advances are encouraged, including application of the requirements of Part 11 regulations.

The staff provides inspection assessments of conformance with current good manufacturing practice requirements for self correction and improvement of operations, and we assist Industry in voluntary recalls of products from the market and in the investigation, evaluation, and corrections of the conditions and practices which led to the recalls. CDER provides certificates of conformance with current good manufacturing practice by the Industry for use in facilitating export of US pharmaceutical production to countries with limited regulatory systems, and we provide consultation to industry and coordination of FDA program activities to alleviate drug shortages.

### **Compliance Oversight of Marketed OTC Drugs**

Enforcement of the OTC Drug Review regulations is paramount to maintaining the integrity of the NDA process. Those members of the regulated industry who market their OTC drugs in compliance with applicable monographs expect FDA to eliminate unfair competition from those who ignore monograph requirements.

### **Pharmacy Compounding**

FDA recognizes that pharmacists traditionally have extemporaneously compounded reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. However, FDA believes that a significant number of licensed pharmacies are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is outside the bounds of traditional pharmacy practice. For example, some pharmacies make large quantities of unapproved drug products in advance of receiving a valid prescription for them, or copy commercially available drug products when there is no medical need for a compounded product. Furthermore, some pharmacies have been found to compound drugs that are contaminated or that are dangerously subpotent or superpotent in a manner that can threaten public health. In such situations, FDA may need to take enforcement action in accordance with the Act to protect the public health.

FDA continues to work with state regulatory authorities, providing support as needed for their regulation of pharmacy compounders. FDA has also issued several warning letters and untitled letters to firms, including warning letters to two pharmacies that were compounding fentanyl (a strong opiate) “lollipops” and dispensing them without the labeling and other packaging and patient safety features required for the FDA-approved product. In addition, FDA sought and was granted inspection warrants to inspect two pharmacies to determine whether these pharmacies were engaged in manufacturing operations or were otherwise in violation of the Act. FDA is in the process of revising a draft pharmacy compounding compliance policy guide and plans to hold a public meeting soon to address pharmacy compounding issues.

### **Import Compliance**

FDA components including CDER’s Office of Compliance worked with the field import district offices and the U.S. Customs in developing categories of drug products targeted during "blitz" operations scheduled at different major mail import centers. These "blitz" operations are held cooperatively with CBP to identify the type and origin of drug products being offered for import into the U.S. through the mail, with emphasis placed on counterfeit, misbranded, adulterated, and restricted distribution drug products. CDER also responds to inquiries concerning import and export regulations and enforcement policy from the regulated industry, consumers, consultants, and health care professionals.

Other inquiries come from field import offices concerning importation of unapproved and investigational drug products, and drugs being imported in advance of application submission and final approval. CDER drafts, reviews, and approves for issuance import alerts which are utilized by various FDA field offices to decide which drugs should be refused entry into the U.S. CDER also interprets the agency's Personal Import Policy (PIP) for other federal agencies such as the DEA and customs. In addition, it handles consumer and small business inquiries concerning the PIP policy.

### **Information Technology**

To support the goal of efficient risk management and to enable the human drugs program, FDA is working to apply information technology by developing and managing systems that provide the FDA with the technical tools to manage the review process and to provide the means to evaluate post-marketing drug safety. The program's Automated Drug Information Management System (ADIMS) is being developed as a fully electronic information management system to receive, evaluate, and disseminate information about investigational and marketing submissions for human drugs and therapeutic biologics. With ADIMS, FDA is addressing its electronic document receipt and validation processes and efforts to develop scientific tools that aid submission evaluation, such as tools to review structured clinical data, labeling data, and drug ingredients. Further, the human drugs program leverages the wealth of data in its Adverse Event Reporting System (AERS) to assist medical officers involved in the review process by providing a data mining tool to identify trends in adverse event data.

*Recent FDA/U.S. Customs Import Blitz Exams Continue Reveal Potentially Dangerous Illegally Imported Drug Shipments*

*FDA and the United States Customs and Border Protection Agency announced in January 2004 that their second series of import blitz examinations found 1,728 unapproved drugs, including so-called "foreign versions" of FDA-approved drugs, recalled drugs, drugs requiring special storage conditions, drugs requiring close physician monitoring and drugs containing addictive controlled substances.*

### **EMPOWERING CONSUMERS FOR BETTER HEALTH**

FDA is committed to enhancing our communication methods to prevent any harm to the U.S. public that may occur due to the lack of accurate and timely information about a drug product. The human drug program is engaged in a variety of activities designed to better enable consumers to make informed decisions weighing benefits and risks of FDA-regulated products.

FDA is collaborating with organizations such as the National Patient Safety Foundation on outreach activities targeting consumers to educate them about the safe use of pharmaceuticals. We are collaborating with the National Council for Patient Information and Education, who is leading the private-sector initiative to bring the industry into compliance with P.L. 104-180 which states that by 2006, 95 percent of all individuals should receive useful written medication information with new prescriptions.

CDER is developing education campaigns to disseminate consumer friendly information on drug products to promote the safety and quality of drug products. We are continuing a Generic Drug Education Program aimed at both consumers and healthcare professionals to inform them about the safety, effectiveness and quality of generic drug products.

FDA develops timely press releases that warn the public about potential hazards associated with purchasing particular products from stores or over the Internet. For example, the Agency issued several press releases that advised the public not to purchase products promoted as alternatives to illicit street drugs (street drug alternatives) and not to purchase products with special safety considerations, such as Accutane, over the Internet.

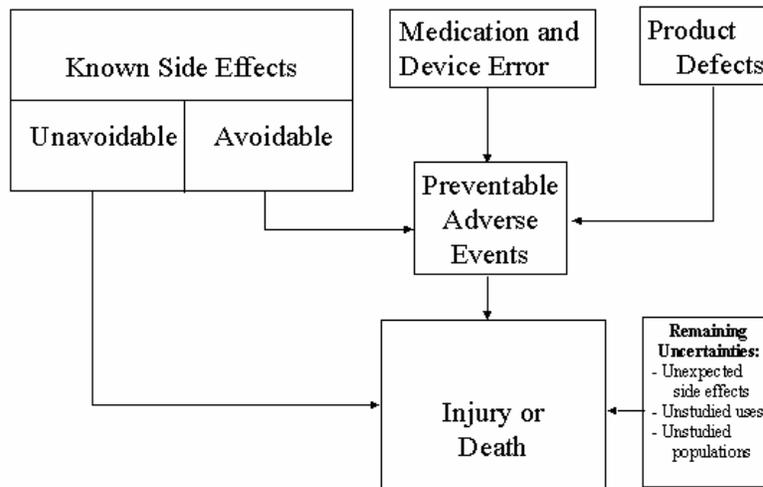
### **PATIENT AND CONSUMER PROTECTION**

The practical size of pre-marketing clinical trials means that we cannot learn everything about the safety of a drug before we approve it. Therefore, a degree of uncertainty always exists about the risks of drugs. This uncertainty requires our continued vigilance to collect and assess data during the post-marketing life of a drug. Once a drug is approved for sale, FDA monitors the use of marketed drugs for unexpected health risks. If new, unanticipated risks are detected after approval, we take steps to inform the public and change how a drug is used or even remove a drug from the market. We also monitor manufacturing changes to make sure they won't adversely affect the safety or efficacy of the medicine. FDA evaluate reports about suspected problems from manufacturers, health care professionals and consumers and tries to make sure that an adequate supply of drugs is always available. FDA also must be vigilant to protect Americans from injuries and deaths caused by unsafe, illegal, fraudulent, and substandard or improperly used products.

CDER monitors the quality of marketed drugs and their promotional materials through product testing and surveillance. As Americans are increasingly receiving the benefits of important new drugs before they are available to citizens of other countries, we must be especially vigilant in our surveillance to prevent fraudulent activities involved with the sale of approved and unapproved prescription drugs. In addition, we develop policies, guidance and standards for drug labeling, current good manufacturing practices, clinical and good laboratory practices and Industry practices to demonstrate the safety and effectiveness of drugs. A comprehensive safety system for medical products is a critical priority. FDA's current systems are not intended to, and cannot, uncover the incidence of adverse events, their preventability, or the overall health and economic impact on Americans. FDA has been partnering with others in DHHS to promote patient safety and prevent medical errors.

FDA's pharmacovigilance program, which is a key component is AERS, provides safety data from this real-world experience. As shown below, the sources of risk from medical products approved by FDA include those that are known ("Known Side Effects"), errors in the use of a medication or device ("Medication and Device Error"), defects in the manufacture of the product ("Product Defects"), and side effects not known at the time of FDA approval ("Remaining Uncertainties").

## Sources of Risk From Medical Products

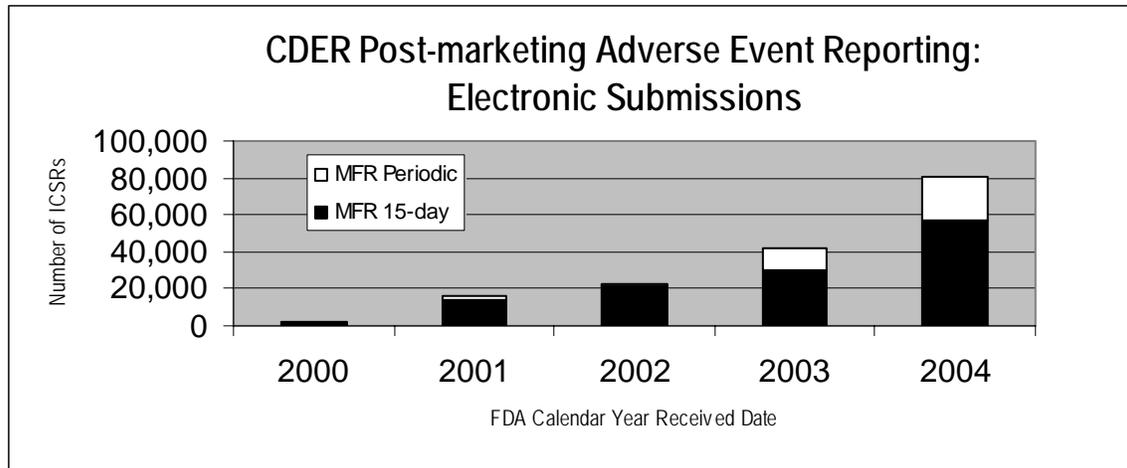


FDA’s ongoing risk assessment, risk management, and risk communication efforts help assure medical product safety in the U.S. Maintaining drug and biologic product quality also helps assure the public that drugs and biologic therapeutics are safe. Pharmacovigilance activities include processing and evaluating reports of adverse drug and biologics events via the AERS database and analyzing epidemiological trends and drug usage in the U.S. that impact drug safety

CDER conducts investigations of reported errors to collect information program managers need to assess the error, and develop error reduction strategies with manufacturers and the medical community. We review adverse event and complaint files at manufacturers during inspections for compliance with FDA reporting regulations and to conduct follow up inspections on adverse event reports when information from the manufacturer is needed to evaluate the risks involved.

CDER operate the MedWatch Program, which permits health care professionals to voluntarily report observed or suspected defects and quality problems associated with marketed drug products. FDA reviews these reports to identify potential health hazards, initiates investigational follow-up, and takes appropriate enforcement action. The Agency reviews hundreds of thousands of reports per year and numerous reports result in product recalls and voluntary corrective actions by industry.

CDER is making progress in encouraging electronic submission of adverse events which save time and money. The graph shows the gradual improvement we are making in electronic receipt of adverse events.



To supplement the adverse event data, FDA is working to establish contracts for safety monitoring data links that include data on product exposure and extensive patient information. The Agency is developing 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.

CDER is involved in a variety of other patient safety-related activities including:

- Working with all interested governmental agencies and private organizations to coordinate collection of adverse event data;
- Monitoring promotion of drug and biologic products to assure the American public that information provided presents a fair balance of risks and benefits and is not false or misleading;
- Identifying health hazards associated with the manufacturing, labeling, and packaging of pharmaceuticals and biologics; removing unsafe and ineffective products from the marketplace;
- Coordinating with Medical Device contractors to continue implementation of drug products into MeDSuN, which is designed to train hospital personnel to accurately identify and report injuries and deaths associated with medical products. This model will be used for both medical device and drug products;
- Providing training for field staff to improve the information gathered through investigation of consumer complaints and reports of medical errors;
- 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 are stimulating a need in the field of biologicals 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 public health crises of global proportions, 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 therapeutic products is detection, identification, and elimination of adventitious agents. One of the chief concerns inherent in biologicals is the potential for the presence of adventitious agents (infectious for humans) in the approved product; and,

- Maintaining reporting systems to collect biological therapeutic product deviation events that occur during manufacturing processes or storage of all biological products;

Further, FDA is continually improving and refining its surveillance efforts by,

- Establishing methods to evaluate the net beneficial impact of risk management plans;
- Seeking appropriate expertise from drug safety leaders in academia, government, trade associations, consumer groups, and industry;
- Assuring the internal use of data standards that are compatible with those used in Government-wide and International initiatives;
- Taking measures (i.e., rulemaking) to increase the number of safety reports submitted electronically;
- Conducting research into quantitative methods of adverse event signal detection;
- Acquiring and developing data systems to detect drug use patterns and practices that enhance safety; and
- Maintaining access to large repositories of population-based health care data for the timely conduct of epidemiologic studies for quantification of safety signals.

### **Human Subject Protection**

FDA takes its role of protecting human subjects involved in clinical trials very seriously. CDER verifies the quality and integrity of data submitted to us to assure patient safety. In addition, the center protects human research subjects who participate in drug studies and assess the quality of data from these studies by conducting annual onsite inspections and data audits by performing on-site inspections of clinical trial study sites, institutional review boards, sponsors, study monitors, and contract research organizations. CDER also conducts inspections to increase oversight of high-risk IND applications and convene conferences of investigators who are the most experienced professionals in the field discuss appropriate monitoring practices.

### **Compliance Oversight of Marketed Prescription Drugs**

FDA continues to protect the public health by assuring that marketed prescription drugs comply with the new drug approval and labeling requirements of the FDCA. This helps ensure that drug products available to the consuming public are safe and effective and labeled correctly to assure their proper use.

Compliance oversight includes review of and providing litigation support for recommended regulatory and legal actions, in both civil and criminal proceedings. It also includes responding to requests for information from both internal and external stakeholders on new drug and labeling compliance issues; preparing assignments to FDA field offices for inspections and investigations and coordinating case development and

compliance actions with regard to new drug and labeling violations; developing and/or reviewing legislative proposals, proposed regulations, policy and guidance documents, enforcement strategies, and outreach activities relating to new drug and labeling compliance issues; and working on a draft compliance policy guidance document that describes how FDA intends to exercise its enforcement discretion regarding certain marketed unapproved drugs.

### **Internet Drug Sales**

At present, there are an exploding number of new web sites marketing FDA regulated products, consumers and medical professionals. FDA monitors potentially fraudulent Internet sites to identify targets for investigation and sampling of products. FDA conducts undercover purchases of prescription drugs from Internet sites suspected of engaging in illicit drug sales, distribution, and/or marketing and we provide oversight of mail and courier packages entering from foreign sources. The Agency uses a risk-based assessment protocol to prioritize and take enforcement action against firms that are illegally marketing products over the Internet. Actions include warning letters, untitled letters, seizures and injunctions.

### **PROTECTING THE HOMELAND -- COUNTERTERRORISM**

FDA plays a critical role in the war on terrorism. Base resources will be used to strengthen the CDER's capability to identify, prepare for, and respond to biological, chemical, and radiological/nuclear threats and incidents. The Program performs the following counterterrorism activities:

FDA is engaged in many efforts to promote the development of medical countermeasures. The Agency encourages early and frequent interactions with sponsors, whether they are developing a novel compound or a new indication for a previously approved product. Regulatory mechanisms, such as Fast Track Designation, use of surrogate markers, or development under the Animal Efficacy Rule, and guidance documents are available to accelerate submission and review. In March 2004, FDA released the "Draft Guidance for Industry: Vaccinia Virus — Developing Drugs to Mitigate Complications from Smallpox Vaccination."

FDA also assesses the potential of new indications for previously approved products where commercial development incentives are lacking. For example, FDA provided funding to an NIH Inter-Agency Agreement (IAG) for the DOD to test the efficacy of several approved antibiotics in non-human primate plague studies. The Agency also provided funding through an IAG with the CDC to conduct human plague trials in Africa, with enrollment that began in the Fall 2004. The funding for both agreements is approximately \$3.5 million and their studies are ongoing. FDA will review these data to conclude whether gentamicin, and perhaps other antibiotics, may receive approval for a plague indication.

FDA is actively working to expand the availability of safe and effective medical countermeasures for special populations (e.g., pregnant or lactating women, infants,

elderly) through contracts that fund pharmacokinetic and safety studies of antibiotics likely to be used to prevent or treat illness following a terrorist attack.

To further stimulate submission of NDA's, FDA gathers pertinent scientific information, analyzes the data, and synthesizes publicly available documents supporting future regulatory applications. In 2003, FDA examined the evidence for Prussian Blue for exposure to radioactive elements that could be released from a "dirty bomb". Since the 1960s, it has been administered to patients as an investigational drug to enhance excretion of cesium and thallium from the body. FDA reviewed the data and literature, determined safety and efficacy, and published this finding, along with draft labeling, to encourage manufacturers to submit marketing applications. Such applications generally require only chemistry and manufacturing information. FDA provides potential sponsors with draft labeling. In October 2003, FDA approved Radiogardase™ (insoluble Prussian blue; Heyl Chemisch-Pharmazeutische Fabrik GmbH & Co) capsules.

*FDA Approves Drugs to Treat Internal Contamination from Radioactive Elements*

*FDA announced the approval of two drugs, pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) for treating certain kinds of radiation contamination. These drugs were approved as part of an ongoing effort to provide the public with the best available protection against nuclear accidents and terrorist threats.*

Patient access to medical countermeasures during a terrorist event is critical. FDA is taking steps to assure that processes are in place if unapproved product is required in response to an event. The National Defense Authorization Act and the recently enacted Project BioShield Act of 2004 provides for Emergency Use Authorization (EUA) where it is reasonable to believe that a product may be effective in the diagnosis, treatment, or prevention of illness from a terrorist agent. FDA is currently prioritizing potential EUA candidates and developing procedures for review of available information. These labor intensive efforts are in addition to the normal drug reviews that encompass FDA's usual business. FDA continues to collaborate with other agencies on the development of INDs to allow access to investigational medical countermeasures. FDA and the CDC are also developing processes for the collection of post-event safety and outcome information on distributed products.

FDA staff participates in a number of committees to facilitate development of medical countermeasures and to provide recommendations on acquisition of products. Inter-Agency groups include subgroups under the White House's Weapons of Mass Destruction Medical Countermeasures Subcommittee and Counterproliferation Technology Coordinating Committee, CDC's Strategic National Stockpile (SNS) Intragovernmental Committee (CDER's representative is a voting member), FDA/CDC Post-Event Surveillance Working Group, Office of Public Health Emergency Preparedness (OPHEP) Smallpox Risk Management Working Group, OPHEP Botulinum Risk Management Working Group, and Second Critical Agents Evaluation and Prioritization meeting in July 2004. Intra-Agency groups include the Inter-Center

Scientific Application of the Animal Rule Working Group, Inter-Center Nuclear/Radiological Countermeasures Working Group, planning group for the Immune Therapies for Anthrax Public Workshop, and CDER Radioeliminators Guidance Working Group.

FDA interacts frequently with the SNS to support the development, availability, maintenance, and deployment of stockpiles of medical countermeasures. FDA provides responses on proposed acquisitions, shelf-life issues, supply and manufacturing inquiries, and regulatory questions. FDA coordinates with the VA, CDC, and SNS on the Shelf-Life Extension Program to extend the shelf-life of stockpiled drugs. FDA released the “Guidance for Federal Agencies and State and Local Governments: Potassium Iodide Tablets Shelf Life Extension” in March 2004.

FDA is also actively involved in emergency preparedness and response activities by participating in exercises that establish appropriate communications procedures for emergency situations. In FY 2004, FDA participated in the international Global Mercury, Federal Government’s Scarlet Cloud, and FDA’s Orange Sunrise and Chem-Bio Response Plan exercises. During 2005 CDER will participate in TOPOFF III. These exercises ensure FDA’s ability to maintain vital operations and service throughout and following terrorist attacks. FDA maintains crisis management plans, including the Continuity of Operations Plan (COOP) that are coordinated and reactive to the Agency crisis management plan, and ensures that personnel are trained in implementation.

FDA through its ORA conducts GMP inspections of drug manufacturing sites whose products are stockpiled as part of the government’s counterterrorism efforts, assures regulated drug and therapeutic biological products are not used as vehicles of terrorism, maintains procedures and plans to ensure the safety and security of personnel, physical assets, and information, and maintains procedures and plans to ensure the safety and security of information technology assets, including essential databases, hardware and networking capacity.

### **IMPROVING FDA’S BUSINESS PRACTICES**

Strong and sound science means Human Drug Program scientists stay on the cutting edge of new technologies. Our mission depends more than ever on a solid cadre of experienced physicians, toxicologists, chemists, statisticians, mathematicians, project managers and other highly qualified and dedicated professionals. The following are examples of activities that fulfill this strategic goal:

#### **E-Government**

The program’s information technology efforts go right to the heart of the PMA for E-Government, by using improved Internet-based technology to make it easy to interact with the government, save taxpayer dollars, and streamline communications. Primarily, the program’s efforts target the following two President’s e-Government Initiatives:

- Government to Business initiatives: to reduce burdens on business, provide one-stop access to information and enable digital communication using XML; and,

- Internal Efficiency and Effectiveness: to advance partnering and end-user focus and to reduce stovepipe systems.

As an example of "Government to Business", FDA has worked diligently with our partners in the International Conference on Harmonization (ICH) on the Common Technical Document (CTD) of the New Drug Application. The CTD provides a harmonized format and content for new product applications in the US, the European Union, and Japan. While the CTD is based on a paper paradigm, the FDA has also worked with our partners in ICH to develop the Electronic Common Technical Document (eCTD) to provide the electronic transmission of CTD applications from applicant to regulator. The eCTD format will replace many of the current electronic submission formats and allow the electronic transmission of applications that currently do not have an electronic solution. Leveraging a common technology across submission types will enhance the review process by allowing the FDA to build a common infrastructure and user interfaces for multiple submission types.

FDA is committed to developing an integrated, fully electronic internet-based or web-capable information management system for receipt, evaluation, and dissemination of human drug safety and effectiveness data coming into the FDA through investigational and marketing applications and related submissions.

This commitment supports both aspects of e-Government mentioned earlier. Specifically, FDA processes an increasing number of electronic drug applications from businesses. Approximately 75 percent of original NDAs received by the Program now include sections submitted electronically and a growing number of these are provided electronically, and this percentage is accelerating. The Program is also committed to several efforts to improve internal efficiency and effectiveness. The program is re-designing and modernizing its internal document and data processing systems used during the drug review process. This modernization also includes consolidating functions, as applicable, with the review of biologic products. The Program is also fully implementing Agency plans for consolidating information technology infrastructure Agency-wide to eliminate the stove-pipe network and desktop equipment and customer service within FDA.

FDA's information technology staff supports the goal for "a strong FDA" by translating the vision of electronic submissions for drug applications and adverse event reports into viable technical systems. The IT staff manage the electronic Common Technical Document (e-CTD) product by gathering requirements for new releases, resolving any technical problems that arise, and implementing new releases. Electronic submissions of adverse event reports, particularly by the pharmaceutical industry, are a top priority for FDA, and an important component of the e-government strategy. The IT staff defines and manages the technical infrastructure that enables electronic submissions of adverse events and is proactively working to increase the number of firms submitting and the technical capacity to handle the move to 100% electronic submissions.

In addition to e-government, IT staff manage many functions such as steady-state system management, contract management of IT systems, project management for new development, and IT security. Further, the staff is responsible for requirements management, configuration management, and system test management for effective development of systems, and development and maintenance of an overarching Enterprise Architecture that integrates business, performance, technology, and data.

## **SELECTED FY 2004 ACCOMPLISHMENTS**

### **USING RISK-BASED MANAGEMENT PRACTICES**

Risk management is at the core of CDER’s mission. Almost everything the center does in the review and approval of Human Drugs relates to weighing the benefits of a product to its risks. CDER’s FY 2004 accomplishments include new, generic, and OTC drugs as well as accomplishments of managing the risks of drugs in the pediatric population.

As the Agency Strategic Plan explains, “efficient risk management” requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry. Accomplishments toward objectives and strategies of the Agency Strategic Plan are included here as well.

### **New Drug Evaluation**

FDA approved several important NDAs in FY 2004 as shown in the table below:

#### **Significant NDAs Approved in FY 2004**

| <b>Drug</b>            | <b>Purpose</b>   |
|------------------------|--|
| Memantine<br>(NAMENDA) | For treatment of moderate to severe Alzheimer’s Disease; this is the first drug approved for the treatment of patients with this severity of disease. Previous treatments for Alzheimer’s Disease have been studied in less severely affected (mild to moderate) patients.   |
| Radiogardase           | Also known as Prussian blue, to treat people exposed to radiation contamination, due to harmful levels of cesium-137 or thallium. Radiogardase capsules contain Ferric (III) hexacyanoferrate(II).   |
| Gleevec                | Received regular approval as a second line treatment for refractory Chronic Myeloid Leukemia (CML), a rare life threatening form of cancer-affecting about 40,000 people in the United States; regular approval means that the FDA has determined that Gleevec has demonstrated a long-term clinical benefit for refractory CML patients. When Gleevec was originally approved under the accelerated approval program in May of 2001, available evidence indicated that a long-term clinical benefit was highly likely but further studies were necessary to confirm it. |

| <b>Drug</b>                  | <b>Purpose</b>  |
|------------------------------|---|
| Alimta (pemetrexed disodium) | For use in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma-a rare type of cancer. Alimta received a priority review and is designated as an orphan drug. It is the first drug approved for this condition. Cancer of the mesothelium, a membrane that covers and protects most of the internal organs of the body is rare; about 2,000 new cases are diagnosed in the United States each year. This form of cancer is usually associated with a history of asbestos exposure. Asbestos fibers lodged in the lung attach to the outer lung lining and chest wall, causing tumors to grow. By the time symptoms appear, the disease is usually advanced, and patients live, on average, nine to thirteen months following diagnosis. |
| Avastin (bevacizumab)        | As a first-line treatment for patients with metastatic colorectal cancer -- cancer that has spread to other parts of the body. Avastin, a monoclonal antibody, is the first product to be approved that works by preventing the formation of new blood vessels, a process known as angiogenesis.  |
| Aldara (imiquimod)           | Aldara (imiquimod) topical cream approved for a new indication. This product is currently approved for the treatment of actinic keratosis and external genital warts. In FY 2004, FDA approved its use for the treatment of superficial basal cell carcinoma (sBCC), a type of skin cancer.   |

#### **NDA's Approved under Accelerated Approval in FY 2004**

| <b>Drug</b>                         | <b>Purpose</b>   |
|-------------------------------------|--|
| Erbitux (cetuximab)                 | To treat patients with advanced colorectal cancer that has spread to other parts of the body. Erbitux is the first monoclonal antibody approved to treat this type of cancer and is indicated as a combination treatment to be given intravenously with irinotecan, another drug approved to fight colorectal cancer, or alone if patients cannot tolerate irinotecan.                                 |
| Vidaza (azacitidine)                | The first effective treatment for patients with Myelodysplastic Syndrome (MDS). The product was given Fast Track Status and a priority review.<br>By restoring normal growth and differentiation of bone marrow cells, this new treatment will offer a much needed option for patients suffering from this rare illness that, in some cases, has been found to progress to leukemia, a type of cancer. |
| Cymbalta (duloxetine hydrochloride) | Capsules for the management of the pain associated with diabetic peripheral neuropathy. This is the first drug specifically approved for this indication.  |

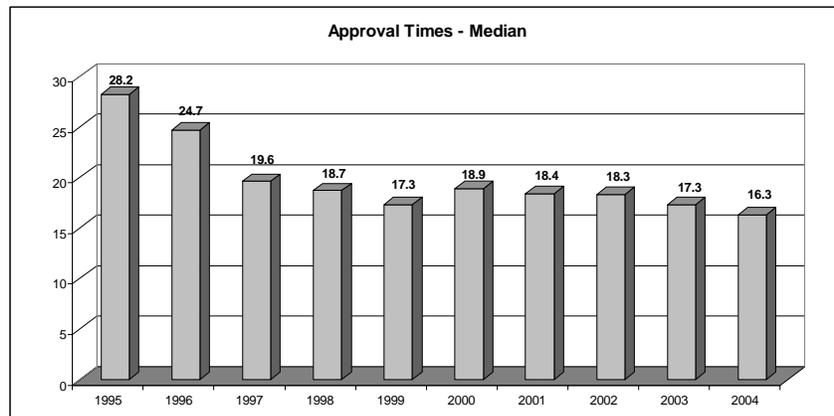
## **Generic Drug Review**

In December of 2003, the President signed the Medicare Prescription Drug, Improvement and Modernization Act of 2003, portions of which provides for more timely approvals of generic drug products. As noted below, OGD has approved greater numbers of generic product thus helping to lower drug costs for millions of Americans. The following are significant generic drugs that will contribute to the goal and assure greater access to affordable health care:

- *Fluconazole Tablets, Injection and Oral Suspension* – Fluconazole is a widely used bis-triazole antifungal agent. There were 41 generic approvals.
- *Benazepril Hydrochloride Tablets* – This is an angiotensin-converting enzyme (ACE) inhibitor drug used to treat high blood pressure. There were 16 generic approvals.
- *Ciprofloxacin Tablets, USP, Injection and Ophthalmic Solution* - Ciprofloxacin is an antibiotic that stops multiplication of bacteria by inhibiting the reproduction and repair of their genetic material (DNA) and may be used for anthrax exposure in the event of a bioterrorist attack. There were 16 generic approvals.
- *Ribavirin* - is used in combination with interferon to treat chronic hepatitis C. As a single source product it was very costly. There were 5 generic approvals.
- *Metformin Extended Release* – Used to treat Type II diabetes.
- *Gabapentin* – Used to treat certain seizure disorders.

The OGD began work on the President’s Emergency Plan For AIDS Relief (PEPFAR). This is a mechanism for FDA to assess the quality, safety, and efficacy of products to treat AIDS in developing nations. The program was initially intended to evaluate only fixed-dose combination products but has expanded to single entities. Several firms have submitted applications and OGD is working with them and others to assure timely action on these applications.

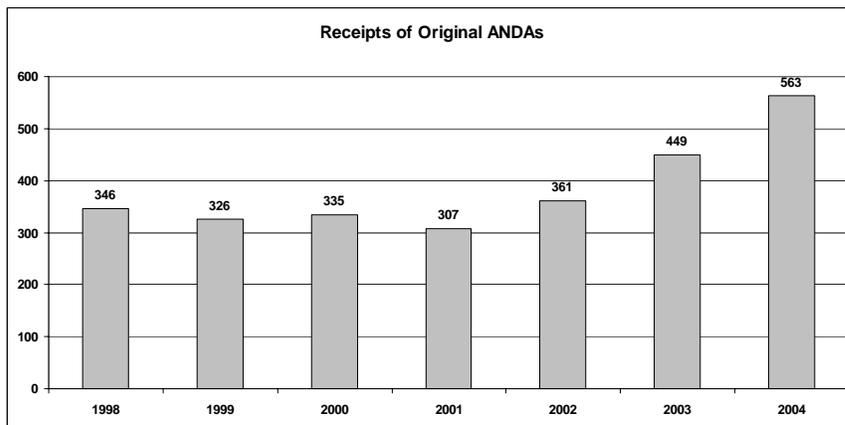
Reviewed and acted on over 91 percent of fileable original generic drug applications within six months of submission and reduced the median approval time from 18.3 months in 2002 to 17.3 in FY 2003 to 16.3 in FY 2004.



The OGD is continually increasing communications with the generic drug industry with a goal of improving the quality of the generic applications thus increasing first cycle approvals and decreasing overall time to approval. Some examples of our outreach to industry include:

- Presented information to the Generic Pharmaceutical Association (GPhA) at the GPhA Fall Technical Workshop;
- Presented two “ANDA Basics” workshops;
- Participated in the GPhA annual meeting;
- Presented several workshops on electronic submissions (CTD/E-CTD);
- Presented a Webcast on Good Manufacturing Practices (GMPs);
- Initiated dialogue on the proposed regulation to require submission of all Bioequivalence studies; and,
- Participated in several telecons with GPhA and the GPhA Technical Advisory Committee.

In FY 2004, the OGD continued to add staff to meet its ever increasing workload demands. A new division of chemistry was established along with an additional bioequivalence review team. There was a 24 percent increase in receipts of original ANDAs from FY 2002 to FY 2003 and an additional 25 percent increase from FY 2003 to



FY 2004. There has also been an emphasis on electronic submissions with just about all submissions having an electronic component.

CDER and OGD remain committed to increasing consumer awareness of the safety and effectiveness of generic drugs and to informing the public about the rigorous review process required for the approval of a generic product. Various public service announcements and advertisements have been used to address this issue.

Staff responsible for the Orange Book has been working to streamline their processes and make the information more readily available. The Orange Book will be available online only thus eliminating the effort expended in publication of the hard copy. The staff has begun daily patent listings and plans additional improvements to assist the health care community.

In FY 2004, FDA began providing more information to the public to help generic drug applicants determine if they are eligible for 180-day marketing exclusivity for their products. This period of marketing exclusivity is generally provided to the first generic

drug that challenges a patent for the innovator product. This marketing exclusivity is an effective incentive for generic drug development provided under the Hatch-Waxman Amendments to the FDCA. With better, more transparent information, generic manufacturers will be able to plan their development of additional generic products more effectively. This step further facilitates the development and availability of generic drugs, which are an increasingly important way to provide the public with safe, effective and affordable medical treatment. In response to two citizen petitions, FDA will now disclose on its website the date on which the first substantially complete generic drug application containing a challenge to a patent listed for the innovator drug was submitted to the agency. FDA had previously posted on the website certain other information regarding generic drug applications.

### **OTC Drug Products**

In FY 2004, the OTC staff approved a total of 6 NDAs. Significant approvals included:

- Claritin Tablets, Syrup, and Reditabs for the treatment of hives, and
- Zantac 150 (higher OTC dose) for the prevention and treatment of heartburn.

Highlights for other significant accomplishments include:

- Approving 6 new efficacy supplements for new product uses;
- Acting on 117 supplement submissions regarding changes to manufacturing procedures;
- Acting on 35 labeling supplement submissions regarding changes to product labeling;
- Conducting 63 meetings with drug companies;
- Publishing 18 Federal Register notices for OTC monographs;
- Answering 12 citizen petitions;
- Completing 4 time and extent applications;
- Answering 9 Congressional Requests including 1 Congressional hearing; and,
- Publishing 1 guidance document and drafting 18 others.

Significant new Federal Register Publications regarding OTC products included publishing proposed rules on revised labeling of sodium content in OTC drugs and revised labeling for cough/cold drug products in the OTC monograph. Further, FDA published a final rule on labeling for calcium, magnesium, and potassium content in OTC drugs anti-diarrhea drug products.

### **Pediatric Drug Studies**

As of September 30, 2004, FDA reviewed 353 Proposed Pediatric Study Requests (PPSR), issued 295 Written Requests for on-patent drugs asking for over 687 studies to be conducted in the pediatric population, and granted exclusivity to 101 out of the 102 products that had a pediatric exclusivity determination. Eighty-two of the 102 products that had a pediatric exclusivity determination had approved labeling incorporating information from the pediatric studies.

In FY 2004 alone, 20 products had pediatric determinations, 19 of which were granted pediatric exclusivity. Twenty-three labels were approved for drugs granted exclusivity. In addition, FDA published 5 abstracts, 6 pediatric labeling articles in the *AAP News*, and 5 articles or book chapters, and participated in 29 outside presentations or liaison activities for various audiences. FDA also has successfully collaborated with NIH as a result of the BPCA. Further, FDA implemented the off-patent process for contracting for pediatric studies and issued 4 Written Requests for off-patent drugs. Other selected accomplishments for FY 2004 in the Pediatrics area include:

- Three Pediatric Advisory Subcommittee and one Pediatric Advisory Committee meetings, where post-pediatric exclusivity adverse events reports were presented on 24 drugs;
- Medical and clinical pharmacology reviews were posted on the pediatric webpage for 22 drugs at the time of action and reviews for 5 SSRI drugs were made public; and,
- One FDA/NIH Newborn Initiative Workshop with over 200 experts in attendance to facilitate drug trials for sick neonates.

### **Information Technology**

A number of initiatives involving data standards were completed in 2004. These data standards allow international harmonization and will be integrated into electronic repositories: Study Data Tabulation Model (SDTM), Annotated ECG waveform data standard, and Structured Product Labeling standard. The data standards support the development of several important tools that will be used in the review process.

### **EMPOWERING CONSUMERS FOR BETTER HEALTH**

In FY 2004, FDA issued draft guidance documents designed to improve communications to consumers and health care practitioners about health conditions and medical products. The guidance is the result of FDA research and policy development, and was influenced by public participation at an open meeting on consumer-directed advertising held by FDA in September 2003. This guidance is evidence that FDA intends to do all possible under the law to make sure that the information conveyed by prescription drug promotion is as useful as possible. This guidance provides new direction to sponsors on how to provide higher-quality health information to the public, based on recent evidence on what works and what does not in drug promotion. The evidence shows that promotions directed to consumers can play an especially important role in helping patients start a discussion with their health care practitioner about conditions that are often unrecognized and therefore under treated, such as diabetes, high blood pressure, high cholesterol, and depression. The draft guidance provides alternatives to the lengthy, detailed, and technically-written "brief summary" of risk information for consumer-directed print advertisements for prescription drugs, with the goal of increasing consumer understanding of the key risks of the product and it provides advice for manufacturers on the use of disease awareness communications, which are designed to educate patients or health care practitioners about particular diseases or health conditions, and do not promote a particular medical product, with the goal of getting more patients to discuss under-treated conditions with their doctor.

As part of its continuing efforts to see that patients and consumers have the information they need to make informed choices, FDA launched a new easy-to-use web site to help consumers and health professionals find information about FDA-approved drug products more quickly and efficiently. The new interface, **Drugs @ FDA** is a searchable database that includes information on approved prescription drugs, some over-the-counter drugs, and discontinued drugs. Located on CDER's web page, it is the first web resource to offer a comprehensive overview of a drug product's approval history. **Drugs @ FDA** makes all drug approval information available on one site so that users no longer have to visit several web pages for information on brand name and generic drugs. The database incorporates information from all parts of CDER's website, including Consumer Information Sheets, Medication Guides, labeling, and other information for patients. Eventually information on recalls, warnings, and drug shortages will also be included. Users can easily search or browse this site by drug name or active ingredient to retrieve a complete approval history and accompanying documents for a particular drug product.

With **Drugs @ FDA**, users can:

- find out if therapeutic equivalents exist including generics for brand name drugs.
- Get the latest FDA information, including consumer-focused information like Medication Guides, for drugs they have been prescribed or that their doctor is considering;
- Identify therapeutically equivalent drugs for prescription medicines, and alternative OTC drugs with the same active ingredient, to help them identify the medicine that is best for them
- Determine whether generic

FDA made great progress in its campaign to inform healthcare providers and consumers about antimicrobial resistance. Many significant accomplishments were made in FY 2004, including:

- Continuing to fund staff responsible for reviewing drug applications associated with antimicrobial drug therapy and antimicrobial resistance, and providing guidance for the development of these products;
- Publishing the final rule for the *Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use* (Vol. 68, No. 25, February 6, 2003, page 6062), by providing information and guidance to the pharmaceutical industry regarding the new labeling requirements for antibacterial drugs to foster appropriate antimicrobial use and reduce the development of drug-resistant bacteria; and,
- Performing additional analyses of antimicrobial resistance in selected bacterial pathogens using data from Focus Technologies. This is year two of a five-year contract with Focus Technologies to monitor and identify current and emerging resistant organisms that pose a significant health threat to the public. The Focus contract allowed FDA to address several Action Items in the *Public Health Action Plan To Combat Antimicrobial Resistance* (<http://www.cdc.gov/drugresistance/actionplan/2002report/index.htm>), including developing a surveillance plan for antimicrobial drug resistance among clinical laboratory isolates to facilitate drug development; reviewing private sector

surveillance data to determine whether the data has potential to support FDA regulatory and scientific activity; and, identifying and evaluating methods for collecting and disseminating the surveillance data on antimicrobial drug use.

FDA launched a national education campaign to provide advice on the safe use of OTC pain relief products. Though pain relievers and fever reducers are safe drugs when used as directed, they can cause serious problems when used by people with certain conditions or those who are taking specific medicines. FDA's nationwide campaign focused on the OTC pain and fever reducers that contain acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which include products such as aspirin, ibuprofen, naproxen sodium and ketoprofen. Many OTC medicines sold for different uses have the same active ingredient. For example, a cold-and-cough remedy may have the same active ingredient as a headache remedy or a prescription pain-reliever. To minimize the risks of an accidental overdose, consumers should avoid taking multiple medications that contain the same active ingredient at the same time. The FDA's consumer educational campaign will include: 1) an OTC pain reliever brochure to be distributed in pharmacies, and by health care providers, 2) a "matte release" newspaper article to be distributed to 10,000 community papers across the country, 3) a reprint of "Use Caution With Pain Relievers", an *FDA Consumer* magazine article that will be distributed at national healthcare conferences and available for reprinting in health related publications and 4) two print public service ads that will be sent to approximately 100 major magazines. All of these materials are available on the web at

<http://www.fda.gov/cder/drug/analgesics/default.htm>

FDA improved its web program for faster posting of generic drug information including information regarding approvals, first generics, tentative approvals, suitability petitions, and other information, and increased our external collaborations to improve information for prescribers and consumers to ensure safe and effective use of generic drugs by:

- Developing and publishing new educational messages in English and Spanish;
- Recording a web-based continuing education program for health professionals;
- Partnering with numerous chain drugs stores (e.g., Walgreens; Eckerds, K-Mart) and third-party payers (e.g., Blue Cross/Blue Shield, Medco) to further disseminate information about the quality and equivalence of generic drug products; and,



- Disseminating information to the public about the quality of generic products through magazine ads, radio spots, advertisements on buses, and similar settings.

## **PATIENT AND CONSUMER PROTECTION**

In FY 2004, FDA issued a final rule requiring bar codes on the labels of thousands of human drugs and biological products. The measure will help protect patients from preventable medication errors and reduce 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 can help doctors, nurses and hospitals make sure that they give their patients the right drugs at the appropriate dosage. 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.”*

This rule calls for the inclusion of linear bar codes -- such as are used on millions of packages of consumer goods -- on most prescription, and most commonly used OTC drugs used in hospitals and dispensed pursuant to an order. Each bar code for a drug will have to contain, at a minimum, the drug's National Drug Code number. This information will be encoded within the bar code on the label of the product. Companies

also may include information about lot number and product expiration dates.

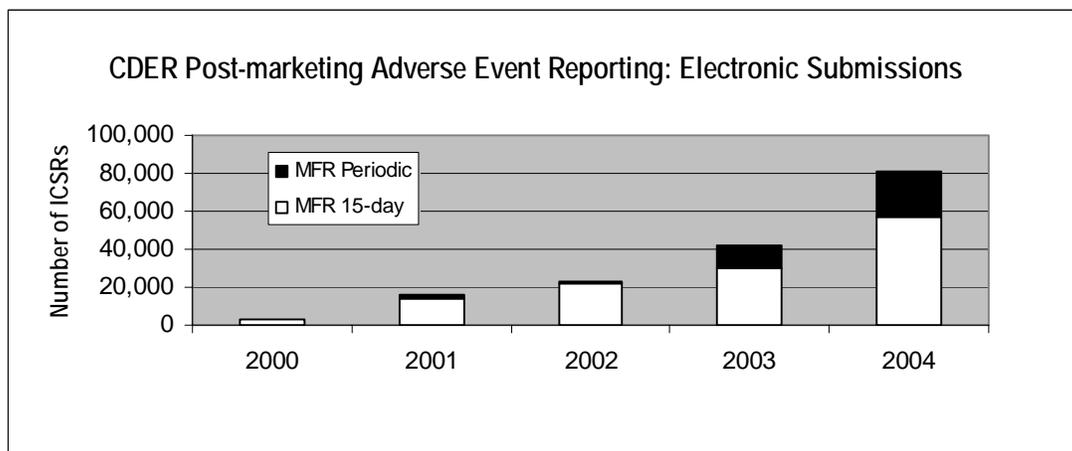
In addition, the rule requires the use of machine-readable information on container labels of blood and blood components intended for transfusion. These labels, which are already used by most blood establishments, contain FDA-approved, machine-readable symbols identifying the collecting facility, the lot number relating to the donor, the product code, and the donor's blood group and type.

The bar-code rule is designed to support and encourage widespread adoption of advanced information systems that, in some hospitals, have reduced medication error rates by as much as 85 percent. In these institutions, patients are provided with identification bracelets that bear a bar code, which identifies the patient. The health care professional then scans the patient's bar code and scans the drug's bar code. The information system then compares the patient's drug regimen information to the drug to verify that the right patient is getting the right drug, at the right time, and at the right dose and route of administration. FDA estimates that the bar-code rule, when fully implemented, will help prevent nearly 500,000 adverse events and transfusion errors over 20 years, with an 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.

The review of adverse event and medication error reports to identify serious or potentially serious outcomes that might be avoided required substantial expenditure of effort. Staff utilized AERS to detect signals. AERS combines the voluntary adverse drug reaction reports from health care professionals and consumers, and required reports from manufacturers and offers paper and electronic submission options, international

compatibility, and pharmacovigilance screening. As we discover new knowledge about a drug's safety profile, we make risk assessments and decisions about the most appropriate way to manage any new risk or new perspective on a previously known risk. Risk management methods may include new labeling, drug names, packaging, "Dear Health Care Practitioner" letters, education or special risk communications, restricted distribution programs or product marketing termination.

Electronic submissions of adverse experience reports provided FDA and the public with several tangible benefits. Specifically, automating the receipt and processing of safety reports will allow the Agency to be more responsive to public health issues, reduce resources associated with data management, and apply better data and better science to the drug regulatory process. The chart below shows the progress we are making in receiving electronic submissions for adverse event information (individual case safety reports (ICSRs)).



We estimate the cost of receiving a report is cut from \$31 per paper report to \$3 to \$19 per report for those submitted electronically. Approximately 35 percent of expedited individual safety reports were submitted electronically in FY 2004, an increase from approximately 20 percent the previous year.

**Information Technology**

In FY 2004, an important project began on structure product labeling. The overall purpose is to improve patient safety by ensuring that medication information is readily available to health care providers, patients, and the public, in its most up-to-date form. The project is part of a larger initiative called the DailyMed. The *DailyMed Initiative* is a partnership between the FDA, medication manufacturers and distributors, the National Library of Medicine, and healthcare information suppliers.

The concept for the DailyMed Initiative is for FDA to collaborate with medication manufacturers and distributors to maintain detailed information about their products in a form called Structured Product Labeling (SPL). SPL is structured information about a medication contained in an XML file. Up-to-date SPL for each product will be transmitted to the NLM on a daily basis. NLM will provide the SPL along with other

medication information in an electronic repository called the DailyMed. Healthcare information suppliers will be able to use the information from this repository in their computer systems, allowing providers, patients and the public access to reliable, up-to-date information on the medications they use.

The objective of this project is to create the environment that will allow the FDA to generate up-to-date, reliable SPL for all drug products marketed in the U.S. Future phases can potentially concentrate on other FDA regulated products including vaccines, animal drug products, dietary supplements, and medical devices.

### **Inspection and Enforcement Initiatives**

In FY 2004, program staff played a key role in a major agency-wide initiative on "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach," a two-year program that applies to pharmaceuticals, including biological human drugs and veterinary drugs. This year, FDA issued its final report on the cGMP initiative ([http://www.fda.gov/cder/gmp/gmp2004/GMP\\_finalreport2004.htm](http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm)). The report discusses:

- The Agency's completed assessment of the current good manufacturing practice regulations, current practices and the new tools in manufacturing science that will enable a progression to controls based on quality systems and risk management; and,
- Specific steps the Agency has taken and will take to develop and implement quality systems management and a risk-based product quality regulatory system.

FDA also took many other steps in FY 2004 to enhance the consistency and coordination of its drug quality regulatory programs. These accomplishments include:

- Piloting a risk-based computer model for prioritizing cGMP inspections for domestic manufacturing sites, in order to further a systematic risk-based approach to inspectional oversight of pharmaceutical manufacturing;
- Training and certifying a Pharmaceutical Inspectorate, a select cadre of field inspectors who will specialize in pharmaceutical pre-approval and cGMP inspections;
- Issuing a final guidance on aseptic processing used in the manufacturing of sterile drugs, thereby encouraging the adoption of modern science and technology and risk-based approaches; and,
- Actively collaborating internationally on pharmaceutical manufacturing issues, in order to move towards implementation of an internationally harmonized plan for a pharmaceutical quality system based on an integrated approach to risk management and science.

FDA also took many other compliance and enforcement steps to protect the American public, including:

- Providing regulatory support to the work of the Strategic National Stockpile (SNS) which is charged with delivering critical medical assets to the sites of

national emergencies. Agency support for the SNS included reviewing the labeling and approval status of stockpile drugs;

- Using a risk-based selection process to choose establishments for inspections to assess compliance with regulatory requirements for adverse drug safety event reporting; and,
- Increasing industry awareness of post-marketing adverse event reporting requirements through an industry education program and development of a public website.

## **PROTECTING THE HOMELAND -- COUNTERTERRORISM**

The Program plays a key role countering terrorism in the U.S., especially in preparing the country to have medical counter measures readily available in the event of any chemical, biological, or nuclear attack. In FY 2004, many accomplishments were made in the area of medical countermeasures. Several new medical countermeasures including five new drug and 15 generic drug applications with counter-terrorism indications were approved. These included the following:

- **Radiation:** Radiogardase (insoluble Prussian blue) capsules were approved to treat people exposed to radiation contamination from harmful levels of cesium-137 or thallium, October 2003. Pentetate calcium trisodium injection (Calcium DTPA) and pentetate zinc trisodium injection (Zinc DTPA) were approved for the treatment of internal contamination with plutonium, americium, or curium, August 2004.
- **Chemical:** The Pediatric AtroPen infant atropine autoinjector was approved, September 2004. This product was developed as part of a post-marketing commitment for approval of pediatric atropine products for older children. The infant atropine autoinjector uses the EpiPen, Jr auto injector device.
- **Biological:** Fifteen new generic drug products for ciprofloxacin and new labeling for Procaine PenG were approved in FY 2004, including the inhalational anthrax, post-exposure, indication.

***FDA Approves First New Drug Application for Treatment of Radiation Contamination due to Cesium or Thallium***

*FDA approved a New Drug Application for Radiogardase, also known as Prussian blue, to treat people exposed to radiation contamination, due to harmful levels of cesium-137 or thallium. Radiogardase capsules contain Ferric (III) hexacyanoferrate(II).*

*The approval of Radiogardase is part of FDA's continuing efforts to provide the*

Additionally, FDA/CDER is actively participating on inter-agency working groups (e.g. WMD MCM Drug Subgroup) related to animal models and testing protocols for radiation/nuclear and chemical agents. FDA's staff directly collaborates with DHHS OPHEP on specific issues related to radiation/nuclear and chemical agents.

FDA, along with DHHS OPHEP, participates in a number of subgroups and working groups of the Weapons of Mass Destruction Medical Countermeasures Subcommittee, which reports directly to White House offices such as the Policy Coordinating Committee. These subgroups and their working groups, with membership from a number of governmental agencies, have been tasked with providing and discussing information that will lead to the development of requirements documents for medical countermeasures to be procured under Project BioShield or other discretionary funds for placement in the Strategic National Stockpile.

FDA/CDER is actively participating on interagency working groups (e.g., WMD MCM Drug Subgroup) related to animal models and testing protocols for radiation/nuclear and chemical agents. In addition, FDA's staff directly collaborates with OPHEP on specific issues related to radiation/nuclear and chemical agents.

In addition, FDA is involved in the following partnership activities:

- DHHS Anthrax Risk Management Working Group to address development of anthrax interventions under Project BioShield;
- An Intercenter Nuclear/Radiation Countermeasures Working Group to facilitate progress of countermeasures by developing a list of potential products currently under development throughout FDA and by sharing common scientific issues across centers;
- Assessing the potential of new indications for previously approved products where commercial development incentives are lacking. For example, FDA provided funding to an NIH Inter-Agency Agreement (IAG) for the DOD to test the efficacy of several approved antibiotics in non-human primate plague studies. The Agency also provided funding through an IAG with the CDC to conduct human plague trials in Africa, with enrollment that began in the Fall 2004. The funding for both agreements is approximately \$3.5 million and their studies are ongoing. FDA will review these data to conclude whether gentamicin, and perhaps other antibiotics, may receive approval for a plague indication;
- FDA, CDC, and the Department of Homeland Security continued efforts to address issues on procurement and use of products in the Strategic National Stockpile;
- DHHS' Office of Public Health Emergency Preparedness' (OPHEP) Smallpox Risk Management Working Group to address development of smallpox vaccines under Project BioShield;
- OPHEP's Botulinum Risk Management Working Group to address development of Botulinum treatments and vaccines under Project BioShield;
- DHHS/OPHEP: Smallpox Risk Management Working Group to address development of smallpox vaccines under Project BioShield; and,
- DHHS/OPHEP: Botulinum Risk Management Working Group to address development of Botulinum treatments and vaccines under Project BioShield.

**Human Drugs  
CDER Program Activity Data**

| <b>PROGRAM WORKLOAD AND OUTPUTS</b>                                      | <b>FY 2004<br/>Actual</b> | <b>FY 2005<br/>Estimate</b> | <b>FY2006<br/>Estimate</b> |
|--|---------------------------|-----------------------------|----------------------------|
| <i>New Drug Review</i>   |                           |                             |                            |
| Priority New Drug Application (NDA) Reviews                              | 31                        | 30                          | 30                         |
| Standard NDA Reviews   | 159                       | 165                         | 165                        |
| Priority NDAs Approved   | 19                        | 16                          | 16                         |
| Standard NDAs Approved   | 74                        | 72                          | 72                         |
| Time from Receipt to Approval (mo.s)(mean)-<br>Priority NDAs             | 13.8                      | (8.5)                       | (8.5)                      |
| Time from Receipt to Approval (mo.s)(mean)-<br>Standard NDAs             | 19.7                      | (18.0)                      | (18.0)                     |
| Time from Receipt to Approval (mo.s)(median)-<br>Priority NDAs           | 9.0                       | (6.0)                       | (6.0)                      |
| Time from Receipt to Approval (mo.s)(median)-<br>Standard NDAs           | 12.7                      | (13.5)                      | (13.5)                     |
| NDA Supplemental Reviews   | 3,313                     | 3,300                       | 3,300                      |
|  |                           |                             |                            |
| INDs (Active)  | 12,523                    | 13,000                      | 13,000                     |
| Clinical Pharmacology/BioPharmaceutic Reviews <sup>1</sup>               | 1,402                     | 1,600                       | 1,600                      |
|  |                           |                             |                            |
| Total Original License Application (PLA/ELA/BLA)<br>Reviews <sup>1</sup> | 5                         | 7                           | 7                          |
| PLA/BLA Approvals  | 5                         | 5                           | 5                          |
| License Supplement (PLA/ELA/BLA) Reviews <sup>1</sup>                    | 272                       | 220                         | 220                        |
| Commercial IND/IDE Receipts  | 84                        | 80                          | 80                         |
| IND/IDE Amendments Receipts <sup>2</sup>                                 | 8,313                     | 8,800                       | 8,800                      |
|  |                           |                             |                            |
| <i>Generic Drug Review</i>   |                           |                             |                            |
| Abbreviated New Drug Application (ANDA)<br>Actions <sup>4</sup>          | 1,536                     | 1,417                       | 1,417                      |
| ANDA Approvals   | 413                       | 399                         | 399                        |
| Average Review Time from ANDA Receipt to<br>Approval (mos.)              | 20.5                      | (18.0)                      | (18.0)                     |
| ANDA Supplemental Actions <sup>5</sup>                                   | 4,630                     | 4,971                       | 4,975                      |
|  |                           |                             |                            |
| <i>Over-the-Counter Drug Review</i>                                      |                           |                             |                            |
| OTC Monographs Under Development <sup>6</sup>                            | 26                        | 15                          | 15                         |
| OTC Final Monographs Published   | 6                         | 11                          | 11                         |
| Establish OTC Consumer Behavior Research<br>Contracts                    | N/A                       | 1                           | 1                          |
|  |                           |                             |                            |
| <i>Best Pharmaceuticals for Children Act</i>                             |                           |                             |                            |
| Approved Labels with New Pediatric Information                           | 23                        | 22                          | 22                         |

| <b>PROGRAM WORKLOAD AND OUTPUTS</b>   | <b>FY 2004<br/>Actual</b> | <b>FY 2005<br/>Estimate</b> | <b>FY2006<br/>Estimate</b> |
|---|---------------------------|-----------------------------|----------------------------|
| <i>Patient Safety</i>   |                           |                             |                            |
| Adverse Reactions Reports   | 458,427                   | 473,586                     | 535,152                    |
| Percentage of Adverse Drug Reaction Reports Submitted Electronically (% of total)       | 15%                       | 65%                         | 75%                        |
| Percentage of Serious/Unexpected Adverse Drug Reaction Reports Submitted Electronically | 29%                       | 65%                         | 95%                        |
| Drug Quality Reporting System Report  | 3,421                     | 2,800                       | 2,800                      |

1/reviews reflect NDAs and supplements and CDER conducted an additional 1382 for INDs in FY 2004.

## 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   |
|--|---|
| <p><b>Improve the efficiency and effectiveness of the new drug review program to ensure a safe and effective drug supply is available.</b><br/>(12001)</p> <p>(Formerly: Ensure a safe and effective drug supply is available to the public.)</p>  | <p>FY 06: Review and act upon 90% of original standard NDAs within 10 months of receipt. Review and act upon 90% of original priority NDAs within 6 months of receipt.</p>  |
| <p><b>Increase the number of drugs that are adequately labeled for children and ensure the surveillance of adverse events in the pediatric population.</b><br/>(12026)</p>   | <p>FY 06: Issue at least 10 written requests (WRs) for drugs that need to be studied in the pediatric population and report to the pediatric advisory committee on adverse events for at least 10 drugs that receive pediatric exclusivity.</p> |
| <p><b>Improve the efficiency and effectiveness of the generic drug review program to ensure safer and more effective generic drug products are available for Americans.</b> (12003)</p> <p>(Formerly: Ensure safe and effective generic drugs are available to the public.)</p>  | <p>FY 06: Decrease the average FDA time to approval or tentative approval for the fastest 70% of original generic drugs applications by 0.5 months.</p>   |
| <p><b>Improve the efficiency and effectiveness of the over-the-counter (OTC) drug review program to ensure a safe and effective drug supply is available.</b> (12048)</p> <p>(Formerly: Increase the number of drugs adequately labeled available for OTC use)</p>   | <p>FY 06: Complete review and action on 100% of Rx-to-OTC Switch applications within 10 months of receipt. Make significant progress on completing 6 OTC monographs.</p>  |
| <p><b>Enhance the protection of the American public against the effects of terrorist agents by facilitating the development of and access to medical countermeasures, providing follow-up assessments on therapies, and engaging in emergency preparedness and response activities.</b> (12045)</p> <p>(Formerly: Facilitate development and availability of medical countermeasures to limit the effects of the intentional use of biological, chemical, or radiologic/nuclear agents.)</p> | <p>FY 06: Coordinate and facilitate development for at least 6 medical countermeasures.</p>   |

| Performance Goals   | Targets  |
|---|--|
| <p><b>Improve the Safe Use of Drugs in Patients and Consumers</b> (12007)</p> <p>(Formerly: Enhance postmarketing drug safety.)</p> | <p>FY 06: Review and provide comments on 100% of Risk Minimization Action Plans (RiskMAPs) for NMEs and for those products for which the sponsor or FDA initiated discussions, in accordance with applicable PDUFA goal dates.</p> |