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FY 2012 Innovative Drug Approvals

Bringing Life-saving Drugs to Patients Quickly and Efficiently

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

Executive Summary

The Food and Drug Administration (FDA) continued to bring life-saving drugs to patients in the U.S. quickly and efficiently in fiscal year (FY) 2012 (October 1, 2011-September 30, 2012). Matching its performance in FY 2011, FDA approved 35 novel medicines in FY 2012, often more quickly than it was done anywhere else in the world. At the same time, FDA continued to strengthen its ability to rapidly detect and analyze safety problems that emerge after a drug is marketed. FDA also broadened the actions it is taking to support innovation in drug development.

The 35 novel drugs approved in FY 2012 included a groundbreaking treatment for a form of cystic fibrosis, the first human cord blood product ever approved, and the first drugs to treat advanced basal cell carcinoma (a form of the most common skin cancer) and the bone marrow disease myelofibrosis. The list includes a total of 10 drugs to treat cancer, as well as important new therapies for HIV and macular degeneration, which causes vision loss and blindness in older patients. Two of the drugs represent advances in personalized medicine, the developing science that uses genetic or other biomarker information to identify patients most likely to respond to a specific treatment. These approvals also include nine new drugs for orphan diseases, continuing FDA's commitment to approving drugs for patients with rare conditions.

As in FY 2011, the 35 approvals of novel drugs in FY 2012 were notable for their efficiency and timeliness. Most of the drugs were approved for U.S. patients before they were available in other countries, and the efficiency of the drug review process continued to grow. For example:

- Of the 32 novel drug approvals that FDA was able to compare to approvals in other countries, 75% (24/32) were first approved in the U.S.;
- 77% of the 35 novel drugs were approved on the first cycle of review, i.e., without the need for additional information that would lengthen the approval time; and
- 34 out of the 35 drugs (97%) met the target dates agreed to under the Prescription Drug User Fee Act (PDUFA),[1] surpassing the PDUFA goal of reviewing and acting on 90% of new molecular entities (NMEs)—novel drugs—by their target dates.

FDA expedited the review and approval of over half of these new medicines by using its several review authorities for important new drugs, including Fast Track, Priority Review, and Accelerated Approval. For example, of the 12 drugs that received a Fast Track designation, 75% were approved on the first cycle of review, and of the 10 Fast Track drugs for which FDA was able to make comparisons to approvals in other countries, 100% were approved in the U.S first. Strengthened communication with drug companies early in development and flexible clinical trial designs for drugs for unmet medical needs also enabled drug companies to conduct shorter,

These accomplishments could not have been achieved without the innovations of the biopharmaceutical industry and the dedication and skill of FDA's drug review staff.

smaller, or fewer studies, reducing the length and cost of drug testing.

Other FDA programs also played an important part in achieving these results. For example, PDUFA, which was reauthorized this year, has provided critical resources for improving the quality and timeliness of premarket review of drugs. These accomplishments could not have been achieved without the innovations of the biopharmaceutical industry and the dedication and skill of FDA's drug review staff.

Getting important new drugs to patients is just the first step in FDA's lifecycle approach to drug regulation. Monitoring the safety of drugs once they are marketed is a critical next step. FDA continues to strengthen its ability to monitor drug safety. For example, the Sentinel Initiative is designed to harness a broad network of healthcare databases to detect and understand drug risks. A pilot called Mini-Sentinel, developed by FDA and outside partners, can now access electronic health information derived from 159 million patients and perform rapid assessments when there is an early signal that a marketed drug may have a safety problem. In addition, implementation of the new drug adverse event system, the FDA Adverse Event Reporting System (FAERS), has modernized FDA's ability to process the more than a million adverse event reports FDA receives each year.

To sustain biopharmaceutical innovation and continue to bring life-saving new drugs to patients, the U.S. faces complex new challenges. Increases in research and development expenditures are not being matched by increased discovery of innovative drugs. Serious public health needs, such as autism and Alzheimer's disease, are not yet being met by new drug innovation, despite years of research and investment. An environment that supports pharmaceutical innovation depends not just on efficient FDA review, but on improving the efficiency and success of the earlier stages of drug development.

FDA is therefore helping to streamline the phases of drug development that occur before a drug marketing application is submitted by emphasizing regulatory science. Regulatory science focuses on the development of scientific tools that can bridge the gap between cutting-edge discoveries and real-world diagnostics, treatments, and cures. Regulatory science projects include FDA's work to increase the use of genetic data and qualified biomarkers, which will advance the development of personalized medicine. FDA is also carrying out projects internally and through collaborations with industry, academia, other regulatory agencies, consumers, researchers and others to help increase the efficiency and success of earlier phases of drug development. Together, we believe efforts like these will support 21st century advances in medicine and improve the lives and health of Americans.

Introduction

In fiscal year (FY) 2012, the Food and Drug Administration (FDA) approved 35 novel medicines developed by the biopharmaceutical industry. These 35 novel drugs included a groundbreaking treatment for a form of cystic fibrosis, the first human cord blood product ever approved, the first drugs to treat advanced basal cell carcinoma (a form of the most common skin cancer) and the bone marrow disease myelofibrosis, and the first imaging agent for detecting amyloid plaques in the brain associated with Alzheimer's disease.

FDA believes that Americans should have access to safe and effective therapies as early as possible. As in FY 2011, the 35 approvals of novel drugs in FY 2012 were notable for the efficiency and timeliness of their reviews. Most were approved after a single review cycle and before their approval anywhere else in the world. FDA also continued its high rate of approving drugs on or before the target dates agreed to under the Prescription Drug User Fee Act (PDUFA). All but one of the 35 novel drugs (97%) met PDUFA target dates,[2] surpassing the PDUFA goal of reviewing and acting on 90% of NMEs by their target dates.

FDA accelerated the review and approval of many of these new medicines through its use of its expedited review authorities. To enable drug companies to conduct shorter, smaller, or fewer studies, FDA strengthened communication with drug companies early in development and approved drugs for unmet medical needs using flexible clinical development programs. FDA also continued to strengthen its ability to monitor drug safety and quickly detect and address drug risks that emerge after a drug is marketed, as well as undertook a number of other initiatives to modernize and enhance its drug safety program.

FDA recognizes that it must also help sustain biomedical innovation in the U.S. Although there is much focus on the FDA premarket review phase of drug development, this phase does not represent the most significant hurdle to marketing a new product. More must be done to reduce the cost and improve the success of earlier phases of drug development, particularly the clinical development phase, which is the longest and most expensive. Through its emphasis on regulatory science, FDA is helping to develop scientific tools that can improve the chances that promising drugs will go forward, while helping detect ineffective or unsafe drugs earlier in their development.

This report deals with FDA's approvals of NMEs in FY 2012. For purposes of this report, NMEs are drugs with novel chemical structures as well as biological products that have never been approved in the U.S. to treat any disease; these generally represent the most innovative drugs entering the market. The report uses the term "drugs" to include products approved by both FDA's Center for Drug Evaluation and Research and FDA's Center for Biologics Evaluation and Research. A complete list of the NMEs approved in FY 2012, with key information about the drugs and their approval, can be found in the appendix to this report.

TIMELINESS OF FDA REVIEW

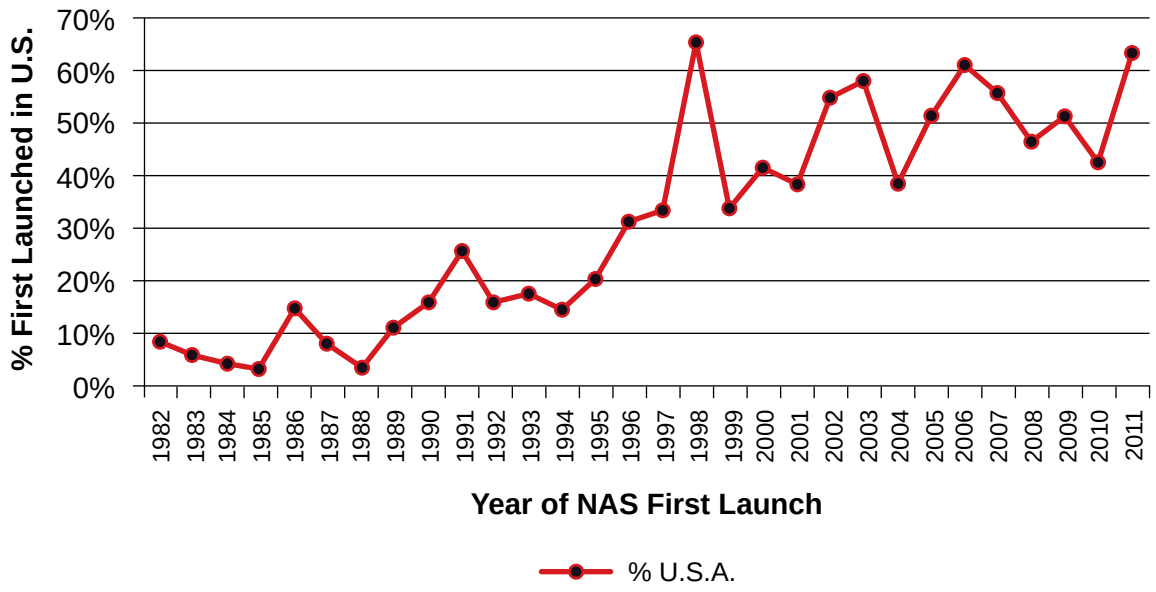
The timeliness of FDA approval of new drugs continues to compare favorably with other regulatory agencies around the world. While we are not in competition with them, we recognize the need to approve safe and effective drugs that offer new health benefits as quickly as possible. As in previous years, FDA's record in FY 2012 shows its commitment to helping patients get timely access to important new drugs.

Figure 1 shows that FDA continues to lead the world in the first introduction of new active substances.[3] This includes all new active substances launched world-wide, including those not approved in the U.S. Over the past decade, roughly half of the new active substances launched anywhere on the world market were first approved in the United States, and the percentage of first introductions in the U.S. is increasing. In 2011, 64% of new active substances were first launched in the U.S., approaching an all-time high for U.S. drug introductions.[4]

Looking only at the 35 NMEs that were approved in the U.S. in FY 2012, the great majority were approved earlier than in other countries. Of the 32 novel drugs for which FDA was able to make comparisons to approvals in other countries, 24 (75%) were approved by FDA before any other regulatory

Figure 1.

U.S. Share of New Active Substances (NAS) First Launched on the World Market



The average length of approval has decreased substantially since the advent of PDUFA in 1992. The median approval time for applications received in FY 1993 was 19.0 months, compared to 9.9 months for applications received in FY 2011.

agency in the world, including the European Medicines Agency (EMA), the European Union's drug approval authority. (Three additional drugs, an imaging agent and two cord-blood products, are manufactured by individual healthcare facilities—a hospital and two blood banks—and it was not possible to determine whether similar products were approved in other countries.)

HOW PDUFA AFFECTS DRUG REVIEWS

Of the 33 novel drugs approved in FY 2011 that were PDUFA products, 32 (97%) met their PDUFA target dates for review. This surpassed the PDUFA goal for FY 2012 of reviewing and acting on 90% of NMEs by their target dates. (Two of the 35 novel approvals were non-PDUFA products, but were reviewed by FDA under PDUFA timeframes; both met their target dates.)

Since its enactment in 1992, PDUFA has had a positive impact on the timeliness of drug review at FDA as well as on our record of first-approvals. The fees collected under PDUFA supplement FDA's resources to hire and train scientific reviewers and keep them abreast of innovative technologies. It also allows FDA to meet with companies early in drug testing and develop guidance documents that clarify the drug development pathway for many diseases. Under PDUFA, FDA and industry also agree on target dates for review of drug applications. The average length of approval has decreased substantially since the advent of PDUFA in 1992. The median approval time for applications received in FY 1993 was 19.0 months, compared to 9.9 months for applications received in FY 2011 (the most recent fiscal year for which we have enough data to provide estimates[5]). The number of new active substances first launched in the U.S. has also risen significantly since PDUFA began (see Figure 1).

HOW FDA EXPEDITES DRUG REVIEW

FDA uses a range of tools to expedite the development, review, and approval of the most promising new therapies. These tools include Fast Track, Priority Review, and Accelerated Approval.[6] Eighteen of the 35 novel drugs (51%) were reviewed under at least one of the Fast Track, Priority Review, or Accelerated Approval programs. FDA also allowed flexible clinical development programs, where appropriate, for drugs for unmet medical needs, such as for orphan

Of the 12 drugs that received a Fast Track designation, 9 (75%) were approved in the first review cycle. Of the 10 Fast Track drugs for which FDA was able to make comparisons to approvals in other countries, 100% were approved in the U.S. first.

drugs. In addition, FDA is beginning to use the "Breakthrough Therapies" provision that was added to FDA's authority this year in the Food and Drug Administration Safety and Innovation Act (FDASIA),[7] but it was not available to expedite any of the drugs approved in FY 2012.

Fast Track

Fast Track, which was developed by FDA, and codified into law in 2007, is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases that will fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious diseases, including AIDS, Alzheimer's disease, cancer, epilepsy, and diabetes. Filling an unmet medical need is defined as providing a therapy where none exists or one that may be potentially superior to an existing therapy.

Once a drug receives Fast Track designation, FDA offers the sponsor early and frequent communications to facilitate an efficient development program. The frequency of communications ensures that questions and issues are resolved in a timely manner, often leading to earlier drug approval. Fast Track drug sponsors are also eligible for "rolling review" of applications, allowing earlier submission and initiation of review. More than a third (12/35) of the 35 drugs were given a Fast Track designation. Of the 12 drugs that received a Fast Track designation, 9 (75%) were approved in the first review cycle. Of the 10 Fast Track drugs for which FDA was able to make comparisons to approvals in other countries, 100% were approved in the U.S first.

Priority Review

In 1992, under PDUFA, FDA agreed to specific goals for improving drug review times and created a two-tiered system of review times—Priority Review and Standard Review. Priority review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. FDA aims to review priority drugs more quickly, in six months versus 10 months for standard drugs. For example, in January 2012, FDA gave a priority review to Kalydeco, a breakthrough drug to treat patients with cystic fibrosis (CF) and who have a specific genetic defect. Kalydeco is the first medicine that targets the underlying cause of CF rather than its symptoms or complications. It was reviewed and approved by FDA in just over three months. Twelve of the 35 FY 2012 drugs received priority review. Of those 12, 11 (92%) were approved on the first cycle, and 10 (83%) were approved in the U.S. before any other country.

More than 80 new products have been approved under Accelerated Approval since the program was established, including 29 drugs to treat cancer, 32 to treat HIV, and 20 to treat other conditions such as pulmonary arterial hypertension, Fabry disease, and transfusion-dependent anemia.

Accelerated Approval

The Accelerated Approval process, first created by FDA in 1992 and later codified in statute, allows approval of drugs that treat serious or life-threatening diseases and that may fill an unmet medical need, based on a surrogate endpoint that is reasonably likely to predict clinical benefit but is not fully validated to do so. In some cases, approval is based on an effect on a clinical endpoint other than survival or irreversible morbidity. A surrogate endpoint is a marker—a laboratory measurement, or physical sign—that is used in clinical trials as an indirect or substitute measurement for a clinically meaningful outcome, such as survival or symptom improvement. For example, viral load is a surrogate endpoint for approval of drugs for the treatment of HIV/AIDS. The use of a surrogate endpoint can considerably shorten the time to approval, allowing more rapid patient access to promising new treatments for serious or life-threatening diseases. Accelerated Approval is given on the condition that sponsors conduct post-marketing clinical trials to verify the anticipated clinical benefit. If these trials fail to demonstrate the anticipated benefits, approval can be revoked.

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Flexible Clinical Development Programs

Several of the drugs for serious diseases without satisfactory alternatives were approved on the basis of non-traditional clinical trial designs or drug development programs. For example, some of these drugs were approved on the basis of a single compelling study or studies using very small patient populations.

Reliance on flexible drug development programs is of particular value in approving drugs for patients with rare diseases—those affecting fewer than 200,000 people in the U.S. Orphan drug therapies for rare diseases represent the most rapidly expanding area of drug development, yet they can be among the most difficult to study. Because of the small numbers of patients who suffer from each disease, FDA often allows non-traditional approaches to establishing safety and effectiveness.

For example, in January 2012, FDA

Approximately one-third of the NMEs approved in the last five years have been drugs for rare diseases. In FY 2012, FDA approved 9 NMEs for rare diseases.

approved Voraxaze, the first drug to treat the small population of cancer patients who develop toxic methotrexate levels in their blood. Patients receiving high doses of methotrexate for cancer chemotherapy may develop kidney failure, making it difficult for them to eliminate methotrexate from their blood. Voraxaze was shown to be effective in reducing methotrexate levels based on data in 22 patients from a single clinical trial.

Although each rare disease affects a relatively small population, rare diseases collectively affect about 25 million Americans. Approximately one-third of the NMEs approved in the last five years have been drugs for rare diseases. In FY 2012, FDA approved 9 NMEs for rare diseases.

Breakthrough Therapies

FDASIA gave FDA a new tool to expedite the development of therapies that show substantial promise in early clinical trials. This new authority arose out of discussions between FDA, the National Institutes of Health (NIH), industry, academia, and patient groups on how to create a novel pathway for development of breakthrough therapies. A drug company may seek designation of a drug as a "breakthrough therapy" if it is for a serious and life-threatening disease and preliminary clinical evidence shows the drug may offer substantial improvement over existing therapies. Once FDA designates a drug as a breakthrough therapy, it will provide advice and interaction throughout the development process to streamline the drug's clinical trials and review. Under FDASIA, FDA has 18 months to issue guidance on how it plans to implement the breakthrough therapy provision, but companies may begin to seek the designation right away. The breakthrough therapy provision was not available to expedite any of the drugs approved in FY 2012.

INNOVATIONS IN DRUG SAFETY

FDA has a dual responsibility: to help Americans get timely access to innovative and life-saving drugs, and at the same time to make sure that the drugs they take are safe. As FDA strives to maximize the efficiency of drug development, review, and approval, the Agency continually works to strengthen its ability to identify, resolve, and prevent drug safety issues. In parallel with improved efficiency in the premarket review process, FDA has devoted substantial resources to strengthening its post-marketing drug safety program.

The development of FDA's Sentinel Initiative is a particularly notable advance in our ability to monitor drug safety. The Sentinel Initiative's surveillance pilot, Mini-Sentinel, is a cutting-edge electronic system that provides access to databases containing information on the effects of drugs in 159 million patients. Access to this information helps FDA detect and analyze new drug risks with improved speed and reliability.

FDA carefully monitors the safety profiles of newly approved drugs, and reassesses them at regular intervals.

Sentinel complements the Agency's new FDA Adverse Event Reporting System (FAERS) which collects information reported to FDA about adverse events potentially associated with a medical product. FDA received over a million adverse event reports this year. FAERS, which helps FDA better evaluate trends and make timely and informed decisions about the safety of marketed products, has modernized FDA's processing of these reports. FDA carefully monitors the safety profiles of newly approved drugs, and reassesses them at regular intervals.

Since FDA was given new authority to require post-marketing safety studies in 2007, the Agency has required drug companies to conduct more than 375 studies to address important safety questions that could not be studied before the drug was approved. FDA was also given authority in 2007 to require Risk Evaluation and Mitigation Strategies (REMS) for drugs that could not be found safe and effective unless certain kinds of restrictions were placed on their use, and has used that authority to allow approval of many drugs whose safety required them.

FDA is also committed to improving the safety of medicines used in children. Until a few years ago, drugs were rarely tested in children and there was almost no information in drug labels about the doses for children or the special risks of using them in children. Under legislation enacted in 1997, drug companies are now conducting needed studies in children. With support and guidance from FDA, about 400 drugs have been studied, and dosing and safety information for children have been added to their labels.

Finally, FDA has made its process of addressing drug safety issues more efficient, and broadened its approach to collaborating and communicating about drug safety issues through:

- Process changes that enhance the quality, accountability, and speed of FDA's decisions on how to handle newly discovered drug risks, including prioritization of drug safety issues and timelines for safety decisions;
- Coalitions built by FDA involving many sectors of the healthcare community to identify and tackle sources of preventable harm from drugs, such as medication errors; and
- Earlier and better communication to the public about potential drug risks as they emerge.

These drug safety initiatives help FDA protect American patients from unsafe drugs. At the same time, they help sustain worldwide confidence in the quality and rigor of FDA's drug program.

For more detailed information on FDA's initiatives to strengthen its drug safety program, see *Advances in FDA's Safety Program for Marketed Drugs*, released in April 2012.[8]

FDA approved 35 NMEs in FY 2012. Of these 35 novel drugs, 15 were particularly notable for their significant contributions to the health and quality of life of patients. FDA reviewed these important drugs quickly, making almost all of them available to patients earlier than in the rest of the world. All but one (93%) of the 14 notable drugs for which FDA could make comparisons to approvals in other countries[9] were approved in the U.S. before they were available in any other country. Twelve of the 15 notable drugs (80%) were approved on the first cycle of review. And all but one of the 15 (93%) met PDUFA target dates for approval. The proportion of these drugs from small biopharmaceutical companies is also significant. Many are the companies' first-approved products. Notable drugs from small companies include Eylea for macular degeneration, Kalydeco for cystic fibrosis, Jakafi and Xtandi for cancer, and Elelyso for Gaucher disease.

CANCER

1. Erivedge (vismodegib) for late-stage skin cancer

Importance: Erivedge is the first FDA-approved drug for late-stage (metastatic) basal cell cancer, the most common form of skin cancer. Basal cell cancer is generally a slow-growing and painless form of skin cancer that starts in the top layer of the skin (epidermis). The cancer develops on areas of skin that are regularly exposed to sunlight or other ultraviolet radiation. Although metastatic basal cell cancer is rare, it is frequently fatal. Erivedge is a pill taken once a day and works by inhibiting the Hedgehog pathway, a "signaling" pathway between cells that plays a primary role in the development of most basal cell cancers. Improved understanding of molecular pathways involved in cancer, such as the Hedgehog pathway, has enabled the development of targeted drugs for specific diseases. This approach is becoming more common and will potentially allow cancer drugs to be developed more quickly. This is important for patients who will have access to more effective therapies with potentially fewer side effects.

FDA actions to speed drug testing and review: The safety and effectiveness of Erivedge were evaluated on the basis of a single, multi-center clinical study in 96 patients with locally advanced or metastatic basal cell carcinoma. The clinical study's primary endpoint was objective response rate or the percentage of patients who experienced complete and partial shrinkage or disappearance of the cancerous lesions after treatment. FDA did not require a showing that Erivedge improved survival. FDA designated Erivedge as a Fast Track drug and reviewed it under the six-month priority review program. The approval came more than a month before the PDUFA target date.

Safety Issues: The most common side effects observed in patients treated with Erivedge were muscle spasms, hair loss, weight loss, nausea, diarrhea, fatigue, distorted sense of taste, decreased appetite, constipation, vomiting, and loss of taste function in the tongue. Erivedge is being approved with a

Boxed Warning alerting patients and health care professionals of the potential risk of death or severe birth effects to a fetus (unborn baby). Pregnancy status must be verified prior to the start of Erivedge treatment.

Time from submission to approval: 4.7 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Everidge was approved ahead of its PDUFA target date.

2. Xtandi (enzalutamide) for late-stage prostate cancer

Importance: According to the National Cancer Institute, an estimated 241,740 American men will be diagnosed with prostate cancer and 28,170 will die from the disease in 2012. Xtandi was approved to treat men with late-stage (metastatic) castration-resistant prostate cancer that has spread or recurred, even with medical or surgical therapy to minimize testosterone. Testosterone, a male hormone, stimulates prostate tumor growth. Xtandi is in the new class of androgen inhibitors—like Zytiga, which was approved last year—designed to interfere with the ability of testosterone to bind to prostate cancer cells. The need for additional treatment options for advanced prostate cancer continues to be important. Xtandi is the latest treatment to demonstrate its ability to extend prostate cancer patients' lives. The median overall survival for patients receiving Xtandi was 18.4 months, compared with 13.6 months for placebo.

Actions by FDA to speed drug testing and review: FDA designated Xtandi as a Fast Track drug for its potential to treat late-stage prostate cancer. FDA reviewed Xtandi under the six-month priority review program and approved it in only 3.3 months. It was the first approved product for Medivation, the drug maker.

Safety issues: The most common side effects observed in study participants taking Xtandi were weakness or fatigue, back pain, diarrhea, joint pain, hot flush, tissue swelling, musculoskeletal pain, headache, upper respiratory infections, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, difficulty sleeping, lower respiratory infections, blood in urine, tingling sensation, anxiety, and high blood pressure. Seizures occurred in approximately 1% of those receiving Xtandi. FDA has required the manufacturer to carry out a post-market study to assess the safety of Xtandi in patients at increased risk for seizure.

Time from submission to approval: 3.3 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Xtandi was approved ahead of its PDUFA target date.

3. Jakafi (ruxolitinib) for myelofibrosis, a cancer that affects bone marrow

Importance: Myelofibrosis is a rare disease in which the bone marrow is replaced by scar tissue, forcing blood cells to be made in the liver or spleen rather than in the bone marrow. This causes enlarged spleens, pain, anemia, fatigue and other symptoms. Jakafi is the first drug to be approved for patients with myelofibrosis, and the first to decrease patients' symptoms. The first in a new class of drugs called Janus Associated Kinase (JAK) inhibitors, Jakafi inhibits two enzymes involved in the development of the myelfibrosis. Jakafi represents an example of an increasing trend in oncology where a detailed scientific understanding of the mechanisms of a disease allows a drug

to be directed toward specific molecular pathways. The clinical trials leading to this approval focused on problems that patients with myelofibrosis commonly encounter, including enlarged spleens and pain. A greater percentage of patients receiving Jakafi experienced more than a 35 percent reduction in spleen size when compared to patients receiving placebo or best available therapy. Similarly, a greater proportion of patients receiving Jakafi saw more than a 50 percent reduction in their myelofibrosis-related symptoms, including abdominal discomfort, night sweats, itching and bone or muscle pain, than did patients receiving placebo.

FDA actions to speed drug testing and review: FDA designated Jakafi as a Fast Track drug and reviewed it under the six-month priority review program.

Safety Issues: The most serious side effects seen in patients treated with Jakafi include low blood platelet levels (thrombocytopenia), anemia, fatigue, diarrhea, shortness of breath (dyspnea), headache, dizziness, and nausea.

Time from submission to approval: 5.5 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Jakafi was approved ahead of its PDUFA target date.

4. Voraxaze (glucarpidase) to lower toxic levels of the chemotherapy drug methotrexate

Importance: Methotrexate is a commonly used cancer chemotherapy drug normally eliminated from the body by the kidneys. Patients receiving high doses of methotrexate may, however, develop kidney failure. Prolonged exposure to high levels of methotrexate can result in kidney and liver damage, severe mouth sores, damage to the lining of the intestine, skin rashes, and death due to low blood counts. Previously available treatments were not able to prevent toxicity when methotrexate concentrations were above certain levels. Voraxaze is an important new treatment option for cancer patients aimed at preventing these toxicities associated with sustained high levels of methotrexate. Voraxaze, an enzyme, rapidly reduces methotrexate levels by breaking the chemotherapy drug down to a form that can be eliminated from the body. In the pivotal study, Voraxaze eliminated 95% of the methotrexate in all patients.

FDA actions to speed drug testing and review: The effectiveness of Voraxaze, an orphan drug, was evaluated on the basis of a single clinical study of 22 patients, all of whom received the drug. A separate study in 290 patients evaluated safety. FDA designated Voraxaze as a Fast Track drug and reviewed it under the six-month priority review program.

Safety Issues: The most common side effects observed in greater than one percent of patients in the clinical study were low blood pressure (hypotension), headache, nausea, vomiting, flushing, and abnormal sensation (paraesthesia).

Time from submission to approval: 6.0 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Voraxaze was approved ahead of its PDUFA target date.

5. Erwinaze (asparaginase erwinia chrysthemi) for acute leukemia

Importance: In patients with acute lymphoblastic leukemia (ALL), the most common form of childhood cancer, the bone

marrow makes too many lymphocytes, a type of white blood cell. White blood cells help the body fight infection and are formed in the bone marrow. ALL is highly curable with treatments that typically involve asparaginase chemotherapy drugs derived from E. coli, a common bacteria. Some children, however, develop an allergy to these drugs. Erwinaze is the first treatment for patients with ALL who have developed an allergy to E. coli-derived asparaginase and pegaspargase drugs. This is a rare condition. Erwinaze is injected directly into the muscle three times a week and works by breaking down one of the body's protein building blocks (the amino acid asparagine) that is present in the blood, and is necessary for the growth of all cells. Leukemia cells cannot produce this protein building block. When a patient is treated with Erwinaze the leukemia cells die. Normal human cells are able to make enough asparagine for their own needs through biosynthesis and will not be affected by treatment with Erwinaze.

FDA actions to speed drug testing and review: The approval of Erwinaze underscores the FDA's commitment to the approval of drugs for conditions with limited patient populations with unmet medical needs using novel trial endpoints. The safety and effectiveness of Erwinaze was evaluated on the basis of one clinical trial of 58 patients, using a novel trial endpoint. Additional safety data were collected in an "expanded access" trial, which is a special trial created to provide access to the drug to patients who are not in the main clinical trial. FDA designated Erwinaze as a Fast Track drug and reviewed it under the priority review program.

Safety Issues: Side effects associated with Erwinaze treatment include serious allergic reactions (anaphylaxis), inflammation of the pancreas (pancreatitis), high blood levels of liver enzymes (abnormal transaminases and bilirubin), blood clotting, bleeding (hemorrhage), nausea, vomiting and high blood sugar (hyperglycemia).

Time from submission to approval: 12.6 months

First approved in: E.U.

Review cycles before approval: 1

PDUFA target date met: No

6. Stivarga (reborafenib) for late-stage colorectal cancer

Importance: The NIH estimates 143,460 Americans will be diagnosed with colorectal cancer, and 51,690 will die from the disease in 2012. It is the second leading cause of cancer death among cancers that affect both men and women, according to the Centers for Disease Control and Prevention (CDC). Stivarga is the latest colorectal cancer treatment to demonstrate an ability to extend patients' lives and was the second drug FDA approved for patients with colorectal cancer within two months. (Zaltrap is other drug.) Stivarga is a multi-kinase inhibitor that blocks several enzymes that promote cancer growth. It is approved for patients with advanced disease whose cancers have continued to spread after treatment with other drugs. Having additional therapies for colorectal cancer remains an important goal, particularly for those patients with no other options.

Actions by FDA to speed drug testing and review: FDA designated Stivarga as a Fast Track drug and reviewed it under the six-month priority review program. Stivarga was approved a month ahead of its target date.

Safety issues: Stivarga was approved with a Boxed Warning alerting patients and health care professionals that severe and

fatal liver toxicity occurred in patients treated with Stivarga during clinical studies. The most common side effects reported in patients treated with Stivarga include weakness or fatigue, loss of appetite, hand-foot syndrome (also called palmar-plantar erythrodysesthesia), diarrhea, mouth sores, weight loss, infection, high blood pressure, and changes in voice volume or quality.

Time from submission to approval: 5.0 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Stivarga was approved ahead of its target date.

7. Perjeta (pertuzumab) for late-stage breast cancer

Breast cancer is the second leading cause of cancer-related death among women. This year an estimated 226,870 women will be diagnosed with breast cancer, and 39,510 will die from the disease. About 20 percent of breast cancers have increased amounts of the HER2 protein, which can be measured through a genetic test. Perjeta, a new anti-HER2 therapy, was approved to slow disease progression in patients with HER2-positive metastatic breast cancer, when used in combination with two other cancer drugs. Perjeta represents a personalized medicine to treat patients who are determined through a genetic test to have HER2 positive breast cancer. Perjeta extended patients' lives by about 6 months. Perjeta is notable both for its contribution to available therapies for late-stage breast cancer and for the way FDA handled production problems at the drug maker that could have affected the supply of the drug at the time of approval. Rather than delay approval until the problems were fixed, FDA limited its approval to those drug products that had not been affected by those problems. Genentech, the manufacturer of Perjeta, committed to take steps designed to resolve these production issues in a timely manner.

FDA actions to speed drug testing and review: The therapy was reviewed under the agency's six-month priority review program.

Safety issues: The most common side effects observed in patients receiving Perjeta in combination with trastuzumab and docetaxel were diarrhea, hair loss, a decrease in infection-fighting white blood cells, nausea, fatigue, rash, and nerve damage (peripheral sensory neuropathy). Perjeta is being approved with a Boxed Warning alerting patients and health care professionals to the potential risk of death or severe effects to a fetus. Pregnancy status must be verified prior to the start of Perjeta treatment.

Time from submission to approval: 6.0 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes.

8. Bosulif (bosutinib) for chronic leukemia

Importance: Chronic myelogenous leukemia (CML) is a blood and bone marrow disease that usually affects older adults. An estimated 5,430 men and women will be diagnosed with CML in 2012. Most people with CML have a genetic defect, called the Philadelphia chromosome, which causes the bone marrow to make an enzyme called tyrosine kinase. This enzyme triggers the development of too many abnormal and unhealthy white blood cells, interfering with their ability to fight infection. Bosulif works by blocking the signal of the tyrosine kinase that causes the abnormal and unhealthy white blood

cells to grow. With the approval of tyrosine kinase inhibitors, we are seeing improvements in the treatment of CML based on a better understanding of the molecular basis of the disease. Bosulif is intended for patients with chronic, accelerated or blast phase Philadelphia chromosome positive CML who are resistant to or who cannot tolerate other therapies. In the clinical trial, many patients in all groups had significant responses to Bosulif; 55% of those with accelerated CML and 28% of those with blast phase CML had an overall hematologic response with no evidence of leukemia.

FDA Actions to speed drug testing and review: The safety and effectiveness of Bosulif was evaluated in a single clinical trial, and FDA did not require a second trial.

Safety issues: The most common side effects observed in those receiving Bosulif were diarrhea, nausea, a low level of platelets in the blood (thrombocytopenia), vomiting, abdominal pain, rash, low red blood cell count (anemia), fever and fatigue.

Time from submission to approval: 9.6 months

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes. Bosulif was approved ahead of its target date.

CYSTIC FIBROSIS

1. Kalydeco (ivacaftor) to treat a form of cystic fibrosis

Importance: Cystic fibrosis (CF) is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations (defects) in a gene that regulates the flow of salt and water out of the body's cells. Defects in salt and water flow result in the formation of thick mucus that builds up in the lungs, digestive tract and other parts of the body leading to severe lung and digestive problems, as well as other complications such as infections and diabetes. Kalydeco is a breakthrough drug for CF—the first treatment that targets one of the gene defects that is the underlying cause of CF, instead of just treating the symptoms of the disease. About 4% of those with CF, or roughly 1,200 people, are believed to have the specific defect targeted by Kalydeco. Those CF patients whose tests show that they have this defect may gain substantial benefits from Kalydeco, including significantly improved lung function and weight gain.

Kalydeco is an example of the promise of personalized medicine—targeted drugs that treat patients with a specific genetic makeup. Kalydeco is also notable because it was developed jointly between Vertex, the drug company, and the Cystic Fibrosis Foundation. The Foundation helped with some of the drug's development costs, provided researchers with useful insights about the CF patient population and helped in the recruitment of study participants—contributions that were critical to quickly bringing the innovative new therapy to patients. The unique and mutually beneficial partnership that led to the approval of Kalydeco can serve as a model for what companies and patient groups can achieve if they collaborate on drug development.

FDA actions to speed drug testing and review: FDA designated Kalydeco as a Fast Track drug because of its potential to treat an underlying cause of cystic fibrosis, meeting an unmet medical need. FDA also reviewed it under the six-month priority review program.

The drug was approved in only 3.5 months.
Safety issues: The most common side effects of Kalydeco include upper respiratory tract infection, headache, stomach ache, rash, diarrhea, and dizziness. After approval, FDA issued a notification to the cystic fibrosis community about the potential for development of cataracts in children taking Kalydeco, based on recent results from a study of Kalydeco in rats.
Time from submission to approval: 3.5 months
First approved in: U.S.
Review cycles before approval: 1
PDUFA target date met: Yes. Kalydeco was approved ahead of its target date.

HIV

1. Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) for treatment of HIV

About 1.2 million people in the U.S. have HIV, the virus that causes AIDS, and about 50,000 become infected each year, according to the Centers for Disease Control and Prevention (CDC). Stribild is a new once-a-day combination pill that provides a complete treatment regimen for HIV-1 infection in adults who have never been treated for HIV infection. Stribild contains two previously approved HIV drugs plus two new drugs, elvitegravir and cobicistat. Elvitegravir interferes with one of the enzymes that HIV needs to multiply. Cobicistat inhibits an enzyme that metabolizes certain HIV drugs and is used to prolong the effect of elvitegravir. The combination of emtricitabine and tenofovir disoproxil fumarate, approved in 2004 and marketed as Truvada, blocks the action of another enzyme that HIV needs to replicate in a person's body. Results from the clinical studies showed that between 88% and 90% of patients treated with Stribild had an undetectable amount of HIV in their blood, compared with 84% and 87% of patients treated with two alternate drug combinations.

New combination HIV drugs like Stribild help simplify treatment regimens and make them more convenient for patients. Through continued research and drug development, treatment for those infected with HIV has evolved from multi-pill regimens to single-pill regimens. Patients prefer and are more likely to follow simpler regimens.
FDA actions to speed drug testing and review: FDA designated Stribild as a Fast Track drug.
Safety issues: Common side effects observed in clinical trials include nausea and diarrhea. Serious side effects include new or worsening kidney problems, decreased bone mineral density, fat redistribution and changes in the immune system (immune reconstitution syndrome). Stribild's label gives advice to health care providers on how to monitor patients for kidney or bone side effects.
Time from submission to approval: 10 months
First approved in: U.S.
Review cycles before approval: 1
PDUFA target date met: Yes

MACULAR DEGENERATION

1. Eylea (aflibercept) for wet age-related macular degeneration

Wet (neovascular) age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in Americans ages

60 and older. AMD gradually destroys a person's sharp, central vision. It affects the macula, the part of the eye that allows people to see fine detail needed to do daily tasks such as reading and driving. An early symptom of wet AMD occurs when straight lines appear to be wavy. There are two forms of AMD, a wet form and a dry form. The wet form of AMD includes the growth of abnormal blood vessels. Eylea is an important new treatment option for adults with wet AMD, because it can be injected once every 8 weeks (following three loading doses given every 4 weeks), compared to other similar products, which require injections every 4 weeks. Eylea can maintain or improve vision in patients with the disease.

FDA actions to speed drug testing and review: FDA reviewed Eylea under the six-month priority review program.

Safety issues: The most commonly reported side effects in patients receiving Eylea include eye pain, blood at the injection site (conjunctival hemorrhage), the appearance of floating spots in a person's vision (vitreous floaters), clouding of the eye lens (cataract), and an increase in eye pressure.

Time from submission to approval: 9.0 months (PDUFA target date extended by the submission of a late major amendment by the sponsor)

First approved in: U.S.

Review cycles before approval: 1

PDUFA target date met: Yes

ALZHEIMER'S DISEASE

1. Amyvid (florbetapir F18) for imaging β-amyloid plaque in the brain

Cognitive decline refers to a condition where the ability to think and form clear, rational thoughts and decisions has decreased. Cognitive decline can be caused by Alzheimer's disease or by other conditions. Beta-amyloid (β-amyloid) plaques are clumps of β-amyloid protein that form in the brains of patients with Alzheimer's disease and sometimes in patients with other causes of cognitive decline. Until now, the amount of β-amyloid plaques in the brain could only be determined with a brain biopsy or examination of the brain at autopsy. Amyvid is the first imaging agent used to produce Positron Emission Tomography (PET) scans that estimate the brain β-amyloid plaque density in patients with cognitive impairment. A positive scan indicates moderate to frequent plaques. A positive Amyvid scan does not, however, establish a diagnosis of Alzheimer's disease. Although patients with Alzheimer's disease always have an increased brain content of plaque, the test also may be positive in patients with other types of neurologic conditions, as well as in older people with normal cognition. A negative scan may be useful, however, in helping to rule out Alzheimer's disease as the cause of cognitive decline. Amyvid does not replace other diagnostic tests used in the evaluation of cognitive impairment.

FDA actions to speed drug testing and review: FDA reviewed Amyvid under the expedited six-month priority review program.

Safety issues: Safety risks include radiation risk and risks associated with image misinterpretation.

Time from submission to approval: 18.6 months

First approved in: U.S.

Review cycles before approval: 2

PDUFA target date met: Yes

BLOOD DISORDERS

1. HEMACORD (hematopoietic progenitor cells, cord (HPC-C)) to treat blood disorders)

Importance: HEMACORD is the first approved drug made from human umbilical cord blood. It is approved for use in stem cell transplantation for patients suffering from a range of blood disorders. For example, cord blood transplants have been used to treat patients with certain blood cancers and some inherited metabolic and immune system disorders. HEMACORD contains hematopoietic progenitor cells (HPCs) from human cord blood. Cord blood is one of three sources of HPCs used in transplants; the other two are bone marrow and peripheral blood. Once these HPCs are infused into patients, the cells go to the bone marrow where they divide and mature. When the mature cells move into the bloodstream they can partially or fully restore the number and function of many blood cells, including immune function. The use of cord blood hematopoietic progenitor cell therapy offers potentially life-saving treatment options for patients with blood disorders.

FDA actions to speed drug testing and review: To assist manufacturers in applying for approval of certain cord blood products, FDA issued a 2009 guidance document that explained how to obtain approval,[10] and created a Cord Blood Licensure Workshop website. FDA also permitted manufacturers to rely primarily on published literature to establish safety and effectiveness. FDA designated HEMACORD as a Fast Track product.

Safety issues: HEMACORD has a Boxed Warning regarding the risks of Graft Versus Host Disease (GVHD), engraftment syndrome, graft failure, and infusion reactions, each of which may be fatal. Patients who receive HEMACORD should be monitored carefully. A risk benefit assessment, unit selection and administration of HEMACORD should be done under the direction of a physician experienced in hematopoietic stem cell transplantation.

Time from submission to approval: 10 months

First approved in: Not applicable.[11]

Review cycles before approval: 1

PDUFA target date met: Yes.[12]

MENINGITIS

1. Menhibrix (meningococcal groups C and Y and haemophilus b (Hib) tentanus toxoid conjugate vaccine) for prevention of bacterial meningitis and other infections in children

Without vaccination, children younger than two years are susceptible to life-threatening bacterial infections that can invade the blood and lining of the brain and spinal cord, causing meningitis and other life-threatening infections. Meningitis and other infections caused by meningococcal or Hib diseases are particularly dangerous because they often progress rapidly and can cause death or serious, long-lasting health consequences such as blindness, mental retardation, or amputations. Early symptoms for both diseases often are difficult to distinguish from other common childhood illnesses. Menhibrix is a combination vaccine that can be used to prevent potentially life-threatening Hib disease and two types of meningococcal disease in children. It is the

first meningococcal vaccine that can be given in infants as young as six weeks of age.

Safety issues: Common adverse reactions reported after administration of Menhibrix were pain, redness and swelling at the injection site, irritability and fever.

Time from submission to approval: 34.1 months

First approved in: U.S.

Review cycles before approval: 3

PDUFA target date met: Yes

GAUCHER DISEASE

1. Elelyso (taliglucerase) for Gaucher disease

Importance: Gaucher disease is a rare disease that occurs in people who do not produce enough of an enzyme called glucocerebrosidase. The enzyme deficiency causes fatty materials (lipids) to collect in the spleen, liver, kidneys, and other organs. The major symptoms of Gaucher disease include liver or spleen damage, low red blood cell counts (anemia), low blood platelet counts, and bone problems. Elelyso is an injection that replaces the missing enzyme in patients with a confirmed diagnosis of Type 1 (non-neuropathic) Gaucher disease. It was shown to be effective in reducing spleen volume and in improving liver volume, blood platelet counts and red blood cell counts.

FDA actions to speed drug testing and review: Because of the small number of affected patients, the efficacy of Elelyso was evaluated in a total of 56 patients with Type 1 Gaucher disease enrolled in two clinical trials. Many of these patients continued treatment in a longer-term extension study. FDA also designated Elelyso as a Fast Track drug.

Safety issues: The most common side effects reported during clinical studies were infusion reactions and allergic reactions. Symptoms of infusion reactions include headache, chest pain or discomfort, weakness, fatigue, hives, skin redness, increased blood pressure, back pain, joint pain, and flushing. As with other intravenous protein products, life-threatening allergic reactions have been observed in some patients during Elelyso infusions. Other commonly observed side effects observed in greater than 10% of patients included upper respiratory tract infection, common cold-like symptoms, joint pain, influenza, headache, extremity pain, back pain, and urinary tract infections.

Time from submission to approval: 24.2 months

First approved in: U.S.

Review cycles before approval: 2

PDUFA target date met: Yes

To support the innovation that benefits patients and industry … FDA must also help streamline the phases of drug development that occur before a drug marketing application is submitted.

This year FDA celebrated the 50th anniversary of the 1962 Drug Amendments, landmark legislation that helped accelerate the development of modern evidence-based medicine. The law's emphasis on making sure that drug safety and effectiveness were supported by rigorous scientific evidence was instrumental in the large number of breakthroughs to treat serious and life-threatening diseases in the last half century. This progress has brought tremendous health benefits to patients while at the same time stimulating innovation and growth in the pharmaceutical industry. FDA's science-based drug review program became known as the world's "gold standard" and the U.S. pharmaceutical industry became the world's leader in innovative medicines.

This report shows that FDA is still a leader in the quality and speed of its drug review and continues to make most innovative drugs available to patients earlier than other countries. FDA's commitment to further strengthening its drug review process will be aided by the passage earlier this year of FDASIA, which included reauthorization of PDUFA. The new resources and authorities provided by FDASIA will accelerate several of FDA's existing initiatives related to making drug development more efficient, including:

1. Expediting the development and review of breakthrough therapies;
2. Advancing patient-focused drug development, which identifies disease-related outcomes that patients care about, includes them in clinical trials and gives weight to patient perspectives on the trade-offs between benefits and risks;
3. Raising the percentage of drugs that get through the review process in the first cycle, and
4. Increasing communication between FDA and drug companies throughout the drug testing and review process.

To support the innovation that benefits patients and industry, however, FDA must also help streamline the phases of drug development that occur before a drug marketing application is submitted. Fifty years after the 1962 Drug Amendments

Regulatory science … can be a critical link between cutting-edge discoveries and real-world diagnostics, treatments, and cures.

brought forth a new generation of life-saving products, FDA and the biopharmaceutical industry face complex new challenges to make sure that biomedical innovation continues. The cost of bringing new drugs to market has risen significantly. Increases in research and development expenditures are not being matched by increased discovery of innovative drugs. Serious public health needs, such as treatments for autism and Alzheimer's disease, are not yet being met by new drug innovation, despite years of research and investment.

At the same time, basic scientific advances, such as discoveries related to the sequencing of the human genome, have suggested many new targets for drug therapy and substantially increased the potential for developing important new drugs. FDA is committed to helping translate these discoveries into actual treatments, preventive therapies, and cures.

With this goal in mind, FDA has continued to make advances in regulatory science a top priority. Regulatory science is the science needed to assess and evaluate a product's safety, effectiveness, quality, and performance. It can be a critical link between cutting-edge discoveries and real-world diagnostics, treatments, and cures. Regulatory science can help scientists recognize the potential of promising therapies that might otherwise be discarded in the early stages of development. At the same time, it can help save critical time and dollars by making sure we have the tools we need to detect unsafe or ineffective therapies at an early stage.

FDA is supporting a range of activities and programs to improve and streamline drug development, including:

- The enhanced use of genetic data and qualified biomarkers to advance the development of personalized medicine;
- Earlier meetings and communication between FDA and drug-makers, especially those that are small or first-time drug developers. These are among the most successful approaches to shortening drug development;
- Critical Path, an FDA program focused on seeking the development of new tools that can streamline drug development, as well as FDA's own research on medical products;
- Improving the scientific foundations and efficiency of clinical trial designs;
- Implementation of the new pathway for "breakthrough therapies," which will help expedite the development of drugs that are likely to provide a substantial improvement over existing therapies, beginning in the earliest phases of testing;
- "Qualification" of new scientific tools to streamline drug development, of which

over 38 are currently in development, so when they are ready to be used, they can be applied by drug companies during drug development without having FDA reconfirm their suitability in each case;
- Exchange of innovations and information about drug development between FDA, industry, and academic scientists in a non-regulatory venue, through the Voluntary eXploratory Data Submissions (VXDS) Program.[13]

These innovations can decrease drug development time, reduce the cost of clinical trials, and increase the odds of successful drug development.

FDA is also collaborating with industry, academia, other regulatory agencies, consumers, researchers and others to help increase the efficiency and success of drug development. Examples of these collaborations include:

- The Coalition For Accelerating Standards and Therapies (CFAST), a recently launched partnership among the FDA, the Clinical Data Interchange Standards Consortium (CDISC), and the Critical Path Institute (C-Path). C-Path will bring together clinical data expertise from the FDA, the pharmaceutical industry, and the information technology sector, to develop and maintain data standards tailored to individual diseases and therapeutic areas;
- The Predictive Safety Testing Consortium (PSTC), which brings together pharmaceutical companies to share and validate each other's safety testing methods in collaboration with the FDA, the EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA);
- The Clinical Trials Transformation Initiative (CTTI), a public-private partnership founded by FDA and Duke University to identify practices that will increase the quality and efficiency of clinical trials;
- The Biomarkers Consortium, a public-private biomedical research partnership working to discover, develop, and qualify biomarkers to support new drug development, preventive medicine, and medical diagnostics; and
- The international Serious Adverse Event Consortium, a nonprofit organization whose mission is to identify genetic variants useful in predicting the risk of drug-related serious adverse events.[14]

The challenges of sustaining biopharmaceutical innovation and translating scientific discoveries into life-saving medicines are substantial. FDA is only one of many players who must be engaged if we are to meet these challenges, but its accomplishments in bringing novel drugs to market quickly and safely will help create a positive environment for innovation. And FDA will continue to provide leadership in driving regulatory science forward. The totality of these efforts will support 21st century advances in medicine, and improve the lives of Americans.

I. PRIORITY DRUGS

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in U.S.	PDUFA Date Met	Approved 1st Cycle	Sponsor
AMYVID (florbetapir F18)	4/6/12	To estimate beta-amyloid plaque density in brains of patients with cognitive impairment		✓	✓		Avid Radio-pharmaceuticals, Inc. Philadelphia, PA
CHOLINE C 11	9/12/12	For PET imaging of suspected prostate cancer hce		NA	✓	✓	Mayo Clinic PET Radiochemistry Facility Rochester, MI
ERIVEDGE (vismodegib)	1/30/12	For advanced basal cell carcinoma		✓	✓	✓	Genentech, Inc. South San Francisco, CA
ERWINAZE (asparaginase erwinia chrysanthemi)	11/18/11	For patients with acute lymphoblastic leukemia (ALL) and allergy to E. coli-derived asparaginase and pegaspargase chemotherapy drugs	✓			✓	EUSA Pharma (USA), Inc. Langhorne, PA
EYLEA (aflibercept)	11/18/11	For wet, age-related macular degeneration		✓	✓	✓	Regeneron Pharmaceuticals, Inc. Tarrytown, NY
JAKAFI (ruxolitinib)	11/16/11	For the bone marrow disease myelofibrosis	✓	✓	✓	✓	Incyte Corp. Wilmington, DE
KALYDECO (ivacaftor)	11/31/11	For cystic fibrosis patients with G551D mutation	✓	✓	✓	✓	Vertex Pharmaceuticals, Inc. Cambridge, MA
PERJETA (pertuzumab)	6/8/12	For HER2-positive metastatic breast cancer		✓	✓	✓	Genentech, Inc. South San Francisco, CA
STIVARGA (regorafenib)	9/27/12	For metastatic colorectal cancer		✓	✓	✓	Bayer Healthcare Pharmaceuticals, Inc. Wayne, NJ

(Priority Drugs Continued)

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in U.S.	PDUFA Date Met	Approved 1st Cycle	Sponsor
VORAXAZE (glucarpidase)	1/17/12	To treat toxic methotrexate concentrations in plasma of patients receiving chemotherapy	✓	✓	✓	✓	BTG International, Inc. West Conshohocken, PA
XTANDI (enzalutamide)	8/3/12	For metastatic, castration-resistant prostate cancer		✓	✓	✓	Medivation, Inc. South San Francisco, CA
ZALTRAP (ziv-aflibercept)	8/3/12	For metastatic colorectal cancer		✓	✓	✓	Sanofi-Aventis U.S., LLC Bridgewater, NJ

II. STANDARD DRUGS

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in U.S.	PDUFA Date Met	Approved 1st Cycle	Sponsor
AUBAGIO (teriflunomide)	9/12/12	For relapsing forms of multiple sclerosis (MS)		✓	✓	✓	Sanofi-Aventis, U.S., LLC Bridgewater, NJ
BELVIQ (lorcaserin hydrochloride)	6/27/12	For chronic weight management		✓	✓		Arena Pharmaceuticals, Inc. Zofingen, Switzerland
BOSULIF (bosutinib)	9/4/12	For chronic myelogenous leukemia (CML)	✓	✓	✓	✓	Pfizer Inc. New York City, NY
ELELYSO (taliglucerase alfa)	5/1/12	For type-1 Gaucher disease, a rare genetic disorder	✓	✓	✓		Protalix Biotherapeutics Inc. Carmiel, Israel
FERRIPROX (deferiprone)	10/14/11	For iron overload in patients with thalassemia (a genetic disorder causing anemia)	✓		✓		Apopharma, Inc. Toronto, Canada
GINTUIT (allogeneic cultured keratinocytes and fibroblasts in bovine collagen)	3/9/12	For application to vascular wound beds in the treatment of mucogingival conditions		✓	✓	✓	Organogenesis, Inc. Canton, MA
HEMACORD (hemapoietic progenitor cells, cord (HPC-C)	11/10/11	For use in unrelated donor hematopoietic progenitor cell transplantation in patients with certain blood disorders		NA	✓	✓	New York Blood Center, Inc. New York City, NY

(Standard Drugs Continued)

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in U.S.	PDUFA Date Met	Approved 1st Cycle	Sponsor
HPC, Cord Blood (hemapoietic progenitor cells, cord (HPC-C)	5/24/12	For use in unrelated donor hematopoietic progenitor cell transplantation in patients with certain blood disorders		NA	✓	✓	Clinimmune Labs Aurora, CO
INLYTA (axitinib)	1/27/12	For advanced kidney cancer		✓	✓	✓	Pfizer, Inc New York City, NY
KYPROLIS (carfilzomib)	7/20/12	For multiple myeloma	✓	✓	✓	✓	Onyx Pharmaceuticals, Inc., South San Francisco, CA
LINZESS (linaclotide)	8/30/12	For irritable bowel syndrome with constipation (IBS-C)		✓	✓	✓	Forest Laboratories, Inc. St. Louis, MO
MENHIBRIX (Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine)	6/14/12	Combination vaccine to prevent meningococcal disease and *Haemophilus influenzae* type b (Hib) in children		✓	✓		GlaxoSmithKline Biologicals, based in Rixensart, Belgium
MYRBERTIQ (mirabegron)	6/28/12	For treatment of overactive bladder			✓	✓	Astellas Pharma Global Development, Inc. Northbrook, IL
NEUTROVAL (tbo-filgrastim	8/29/12	To reduce duration of neutropenia in chemotherapy patients			✓		Sicor Biotech UAB Vilnius, Lithuania
OMONTYS (peginesatide)	3/27/12	For anemia in chronic kidney disease patients on dialysis		✓	✓	✓	Affymax, Inc. Palo Alto, CA
ONFI (clobazam)	10/21/11	For seizures associated with Lennox-Gastaux syndrome	✓		✓	✓	Lundbeck, Inc. Deerfield, IL
PICATO (ingenol mebutate)	1/23/12	For the topical treatment of actinic keratosis		✓	✓	✓	Leo Pharma AS Ballerup, Denmark
PREPOPIK (sodium picosulfate, magnesium oxide, citric acid)	7/16/12	For colon cleansing in preparation for colonoscopy			✓	✓	Ferring Pharmaceuticals Parsippany, NJ
STENDRA (avanafil)	4/27/12	For the treatment of erectile dysfunction (ED)			✓	✓	Vivus Inc. Mountain View, CA

(Standard Drugs Continued)

Drug Name	Approval Date	Indication	Orphan Drug	Approved First in U.S.	PDUFA Date Met	Approved 1st Cycle	Sponsor
STRIBILD (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)	8/27/12	For treatment of HIV-1		✓	✓	✓	Gilead Sciences, Inc. Foster City, CA
SURFAXIN (lucinactant)	3/6/12	To prevent respiratory distress syndrome (RDS) in premature infants		✓	✓		Discovery Laboratories, Inc. Warrington, PA
TUDORZA PRESSAIR (aclidinium bromide)	7/23/12	For long-term maintenance treatment of bronchospasm in COPD		✓	✓	✓	Forest Laboratories, Inc., St. Louis, MO
ZIOPTAN (tafluprost)	2/10/12	To reduce intraocular pressure (IOP) in patients with glaucoma or ocular hypertension			✓		Merck Sharp and Dohme Corp. Whitehouse Station, NJ

References

1. Two of the 35 novel approvals were non-PDUFA products, but were reviewed by FDA under PDUFA timeframes and met their target dates.
2. Two of the 35 novel approvals were non-PDUFA products, but were reviewed by FDA under PDUFA timeframes and met their target dates.
3. “New active substances” include novel chemical or biological substances not previously approved to treat any disease. There is a close but not complete overlap between NASs and NMEs: NASs exclude radiopharmaceuticals, which are radioactive compounds used in medical diagnosis or treatment.
4. A recent article in the New England Journal of Medicine also compared novel drugs approved by FDA, EMA, and Health Canada on a number of measures including how often each agency was the first to approve a drug. Looking at drugs approved from 2001 through 2010, the authors found that among those drugs approved in both the U.S. and Europe, 63.7% were approved first in the U.S. Among those drugs approved in both the U.S. and Canada, 85.7% were approved first in the U.S. The length of FDA’s review was also shorter than that of either the EMA or Health Canada. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholtz HM, Ross JS, Regulatory Review of Novel Therapeutics-Comparison of Three Regulatory Agencies. N Engl J Med 2012; 366:284-2293. Available online at: http://www.nejm.org/doi/full/10.1056/NEJMsa1200223#t=articleTop.
5. Because these data are based on year of receipt rather than approval, many applications received in FY2012 are still under review and no estimates can be given yet.
6. See http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm.
7. Section 902 of the Food and Drug Administration Safety and Innovation Act of 2012, 21 U.S.C. 356(a).
8. FDA, Advances in FDA’s Safety Program for Marketed Drugs: Establishing Premarket Safety Review and Marketed Drug Safety as Equal Priorities at FDA’s Center for Drug Evaluation and Research. Available online at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM300946.pdf.
9. HEMACORD, a cord-blood product, is manufactured by a single blood bank—and it was not possible to determine whether similar products were approved in other countries.
10. FDA, Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications, Oct. 2009. Available online at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM187144.pdf.
11. HEMACORD was approved for use by a single blood bank, and it was not possible to determine whether there were similar approvals in other countries.
12. Cord blood products are not subject to PDUFA; however, FDA assigns and adheres to PDUFA schedules during review of BLAs for these products.
13. For more information on VXDS, see http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083673.htm.
14. For more information about these and other public-private collaborations, see http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm.