



**Drug Review and Related Activities in the United States
(Revised July 2004)**

TRANSCRIPT

Slide 1 Hello and thank you for visiting the Food and Drug Administration, Center for Drug Evaluation and Research revised course on drug development in the United States.

The Center for Drug Evaluation and Research has undergone a lot of changes since the first time we offered this program in 2000. So if this is your first time viewing this presentation or you are returning to learn more about the changes we have made since last time... welcome. As we take you from laboratory testing through clinical trials by industry, to FDA review, to the time the drug product reaches your local pharmacy, we are going to include new initiatives, and other new program areas that have brought the Center into the 21st century of promoting and protecting the health of the American people.

Slide 2 Let me first introduce myself. I am Brenda Kilianny, a pharmacist in CDER's Office of Training and Communications working with the public with regard to human drug products and drug regulation. My colleague, Mary Krenzner, who is also a pharmacist in our office, will deliver the second part of this presentation.

The goal of today's program is to make information about the human drug regulatory process more clear and understandable.

Slide 3 Upon completion of this presentation, you will be able to fulfill the learning objectives of this course. In short, we will begin by explaining the new drug development and review process in the United States and finish by letting you know where and how to obtain current drug information from the agency.

Slide 4 We have a lot to cover so, let's get started. Throughout the years, Congress has passed many laws that have improved protections and public health for the American people. You can see how FDA's consumer protection responsibilities have grown since 1906 when the original Food and Drug Act was passed. In essence, the original Food and Drug Act prohibited interstate commerce of misbranded and adulterated food, drinks, and drugs.

Subsequent to 1906, the tree shows many of the most significant drug laws to have been written by Congress. For example, in 1938 Congress passed the Federal Food, Drug and Cosmetic Act which, among other things, required that new drugs be shown **safe** before marketing. This Act was passed largely in response to the Elixir Sulfanilamide disaster in

1937 that received national attention. This preparation was distributed without testing for safety (which at that time was not required by law). Because it contained diethylene glycol as a vehicle, a chemical analogue of antifreeze, over 100 people died, many of who were children.

When that was not enough to protect public health, Congress passed another Act in 1962 (the Kefauver-Harris Drug Amendments) which added the requirement that drugs must also be **effective**.

Then in the 1980's Congress promoted research into diseases that only affected small populations by passing the Orphan Drug Act and shortly thereafter saved Americans money by passing the Waxman-Hatch Act which provided for generic drug marketing.

A noticeable addition at the top of our FDA tree timeline is the Public Health Service (PHS) Act, passed in 1944. The PHS Act is the legal basis for licensing of biologic products. In other words, it is the mechanism for marketing approval of a biologic drug product. It requires a U.S. licensing number for biologic drug manufacturers in addition to proving safety and effectiveness. If the difference between a drug and a biologic is unclear to you at this point in the presentation, let me explain.... Biological products are approved for marketing under the provisions of the Public Health Service Act. However, because most biological products also meet the definition of "drugs" under the Federal Food, Drug, and Cosmetic Act (FD&C Act), they are also subject to regulation under FD&C Act provisions.

You will learn throughout this presentation the impact that ALL these laws and Acts illustrated on our tree timeline have had on our lives to improve and protect public health.

Let's start with some background on FDA and its organizational structure to give you a better understanding of each of the Centers' roles and responsibilities. The FDA is one agency in the Department of Health and Human Services; with more than 9,000 employees carrying out its important regulatory mission. Public health protection now includes addressing unprecedented challenges and threats to the health of the public – ones that are more sophisticated and complex than those of the last century.

On **Slide 5** you can see that the FDA is made up of six Centers.

CDRH, or the Center for Devices and Radiological Health, reviews medical devices from needles to x-ray machines.

NCTR, or the National Center for Toxicological Research, conducts research to define biological mechanisms of action underlying the toxicity of products regulated by the FDA. They also develop methods to improve assessment of human exposure and risk. FDA's research activities provide the scientific basis for regulatory actions, guide standard-setting, and develop test methods and other support for product monitoring and to study emerging risks.

CBER, the Center for Biologic Evaluation and Research, reviews products derived from living sources such as humans, animal, plant, and microorganisms. These products are diverse, including blood, vaccines, and gene therapy.

CFSAN, the Center for Food Safety and Applied Nutrition, monitors food products, dietary supplements, and cosmetics.

CVM, the Center for Veterinary Medicine, regulates products used by animals like medicine and feed.

CDER, the Center for Drug Evaluation and Research, is the largest of all the centers with more than 2,000 employees. We regulate human drugs and biologic drug products, which will be our focus for today's presentation.

ORA, the Office of Regulatory Affairs, although not a Center, operates with a field staff greater in size than that of CDER.

Slide 6 ORA consists of 167 Field offices, in district and regional offices throughout the United States. These FDA employees across the country are involved in a number of activities, offering surveillance, domestic and foreign inspections, import activities, sample collection and testing, laboratory work, and education. Additionally, our partnerships with Federal and State agencies, as well as private oversight organizations, help bring more resources and a more coordinated powerful approach to enforcement.

Slide 7 Here is the current organizational structure of CDER, which as I stated earlier, will be our focus today.

The majority of CDER employees are involved in reviewing safety and efficacy data submitted by industry before, during, and after a drug is approved.

The Office of New Drugs, in the left column of the slide, contains six offices of drug evaluation, which we will discuss in greater detail later.

The Office of Pharmaceutical Science, or OPS, contains several offices, which provide the science base for the Center. Some of the offices are involved in the review of new drugs.

The Office of Generic Drugs is in OPS. We will also discuss this office in greater detail later in the presentation.

CDER is responsible for reviewing human drugs, including some biologic therapeutic products whether they are prescription, generic, or over the counter (OTC), for safety and effectiveness before they can be marketed.

CDER is also responsible for monitoring all human drugs and therapeutic biologics once they are on the market, and for taking action, if necessary, to remove products which may not be manufactured properly or may cause harm to the American people. This is no small task, given the thousands of approved products in the United States!

You may be asking yourself why is CDER reviewing drugs AND some biologics if there is a Center for Biologics? Because there are many similarities in the review of drugs and biologic therapeutic products in order to improve our efficiency, as of October 1, 2003, CDER staff is reviewing biologic therapeutic product applications.

I want to emphasize at this point that the FDA does not, on its own, develop new drugs, or perform clinical trials. Yet, we do regulate the development and monitor the safe conduct of clinical trials in partnership with industry.

Slide 8 So what exactly is a drug? The definition of a *new drug*, as it is written in the Federal Food, Drug, and Cosmetic Act of 1938, is any product used to diagnose, cure, mitigate, treat, or prevent a disease. The next slide provides the definition of a biologic.

Slide 9 A biological product is subject to licensure under the Public Health Service Act. It is any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of diseases or injuries to humans.

In contrast to most drugs that are chemically synthesized and their structure is known, biologics are derived from living sources, such as humans, animals, plants, and microorganisms.

Slide 10 I mentioned the Federal Food, Drug, and Cosmetic Act of 1938. FDA gets its authority from Congress to enforce this Act and several other public health laws. Congress writes laws, and regulations are written in response to the law.

The Code of Federal Regulations, or CFR, is the book in which all final regulations are codified. This book which you see pictured here represents how FDA interprets the Acts or laws, which Congress passes.

Each Center uses a portion of the CFR. It is made up of several volumes. CDER regulations are mainly in sections 200 and 300 and for biologic drugs, the 600 series.

These regulations can be purchased in book/hardcopy form or now can be viewed on-line at www.access.gpo.gov.

In addition to the regulations, the Center spends a considerable amount of time and effort writing guidances for industry that help with all areas of drug development, manufacturing, and marketing. These are considered the established recommended practices or current best thinking. They are dynamic and often require public input.

A good example of this is FDA's recent effort to encourage manufacturer innovation; the FDA has released a draft guidance, which describes a regulatory framework to encourage voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance technologies.

Working with existing regulations, the agency has outlined the scientific, risk-based framework called Process Analytical Technologies, or PAT, which should help pharmaceutical manufacturers design, develop, and implement new efficient tools for use during product manufacturing and quality assurance while maintaining or improving the current level of product quality assurance.

Ultimately, our risk-based approach should decrease the likelihood of adverse inspection outcomes, product recalls, and drug shortages.

Slide 11 With a basic understanding of FDA's mission and CDER's organizational framework, I'll begin to explain the new drug review process in the United States.

Every drug and biologic, before receiving approval for marketing in the United States, must undergo rigorous scientific testing and scrutiny to ensure it is safe and effective for its intended use.

It is estimated that 3.1 billion prescriptions will be filled this year in the United States. That is 60 percent greater than 10 years ago. In fact, the process is so commonplace that the tablets, capsules, and other medications that virtually every one of us relies on to restore or maintain good health at some point in our lives come to be taken for granted. Yet these drugs--and the improved quality of health they bring to the American people--are truly "miracles of modern science." In fact, the process for discovering, developing, and testing new drugs encompasses some of the most exciting areas of scientific discovery today.

The drug development process begins when an idea for a new drug product is born. The earliest part of the new drug development process includes the discovery and screening process and pre-clinical research. These stages of development are completed primarily by manufacturers (or sponsors) and researchers.

In the discovery and screening phase, the manufacturer, or sponsor, is looking for a compound that has a desired effect without toxicity. In other words, several thousands of molecular entities are screened, although only a very few make it through clinical trials to the pharmacy shelf. As a matter of fact, the vast majority of treatments that enter clinical testing don't succeed. Only about 20 percent will subsequently receive FDA marketing approval.

There are several methods used to identify compounds for research. Most notably now, researchers are using computers to manipulate chemistry to speed up the discovery process and in some cases test these products on virtual organs or patients.

Slide 12 During pre-clinical research, drug sponsors study a product's chemical properties, develop steps for synthesis and purification, and begin short- and long-term studies in animals. The goal of pre-clinical trials is to gather data to prove the compound is reasonably safe for use in clinical trials or human trials.

In short-term animal studies, the sponsor is looking at how the drug is handled by the body, (the absorption, distribution, excretion) as well as any acute toxicity issues that may arise.

Long-term animal studies will continue throughout the clinical trial period and are more focused on issues of teratogenicity, carcinogenicity, and genotoxicity.

The yellow diamond that you see on this slide indicates an invitation by FDA to meet with the sponsor. All sponsors, at certain intervals during the drug development process, are invited by FDA to meet regarding the progress of their research. The meetings may occur in the pre-clinical phase for a company that is new and unfamiliar with the new drug development process, has never submitted data to FDA before, or perhaps a company who believes the product they are developing deserves to get what we call "fast track" status.

Fast track status means that the product demonstrates the potential to address an unmet medical need for a serious or life-threatening disease. This particular meeting time is used to provide the foundation upon which the product moves into the next stage of development which is clinical trials. The Center has initiated a pilot program where a small number of Fast Track IND's participate in a program of more extensive scientific feedback and interaction during drug development.

CDER has further enhanced the efficiency and effectiveness of the drug development and marketing application review process by piloting another program to expand on the existing *rolling review* process for Fast Track products. New processes have been created to accommodate early submission and review of selected portions of a small number of applications.

These pilot programs will include a comprehensive assessment of their added value, costs, and impact to determine whether such activities can improve the efficiency of the drug development and review process and shorten review time.

Slide 13 Once the pre-clinical research is complete, the drug's sponsor submits to CDER what is called an investigational new drug application, or IND. The IND contains the pre-clinical data including the results of short-term animal studies, and proposed plans for study in a human population.

By law, the Center has 30 days to review the IND. We take this decision very seriously because patient safety is of paramount importance to the FDA. The submitted information is reviewed and a decision is made whether to permit a sponsor to begin trials in humans.

In the clinical studies, products typically undergo three phases of clinical trials.

In **Phase I trials**, the sponsor tests the product's safety usually in a small group of healthy individuals. The emphasis is on the drug's activity in the body, such as absorption, distribution, and excretion. Since safety is the emphasis in this phase, the sponsor is also looking for any toxicity or side effects.

In **Phase II trials**, the sponsor tests the product's safety and effectiveness, as well as the best estimate of the right dose in a larger group of patients. This proper dosing information is based on preliminary estimates of safety and effectiveness. Since effectiveness is evaluated in this phase, the product is introduced to patients who may benefit from its use, patients who have the condition under study (for example, asthma or high blood pressure).

In **Phase III trials**, the sponsor provides "substantial" clinical evidence that the drug is safe and effective. These trials are much larger than Phase II trials, vary in design, and the drug is often given for longer duration. Phase III gathers additional data and evaluates the risk vs. benefit, dosing, and other information contained in the package insert.

Slide 14 is a summary of the three phases. Although the goal of clinical trials is to obtain safety and effectiveness data, the safety of clinical subjects is continually considered by FDA. Our Division of Scientific Investigations is essential in protecting the rights and welfare of human research subjects and verifying the quality and integrity of bioresearch data. This focus on appropriate study conduct and oversight, and compliance with relevant regulations is part of our comprehensive approach designed to monitor all aspects of the conduct and reporting of FDA regulated research.

The results of these trials answer the question "does this drug work for the proposed use?" During a clinical trial, more and more information is gained about a new drug, its risks, and how well it may or may not work.

Slide 15 Let's take another look at the timeline. At the end of Phase II, you once again see the yellow diamond. This is what we call the end of Phase II meeting. This meeting is very important because Phase III studies are typically large, multi-center and expensive trials. The sponsor decides in collaboration with FDA how to approach Phase III trials.

The meeting serves three purposes:

- These meetings can provide expert opinion and advice regarding data from Phase II and plans for Phase III.
- We work proactively with the sponsor to make the drug development process as efficient as possible.
- These meetings speed up the process of drug development so the American people can benefit sooner from drug discovery and research.

Industry and FDA do share a common goal, which is public health.

Slide 16 Some drugs show exceptional promise for treating life-threatening conditions or those for which no satisfactory treatment exists. These drugs may be considered for the Center's accelerated approval or early access programs.

Accelerated approval is a highly specialized program for speeding the approval of promising therapies so that the product can reach the market faster. CDER reviewers base a determination of a product's safety and effectiveness on "surrogate endpoints." A surrogate endpoint can be a laboratory finding or a physical sign that is not in itself a direct measurement of how a patient functions or survives but is likely to predict the drug's therapeutic benefit. For example, tumor shrinkage could be the surrogate for increased survival. As a condition of approval, however, FDA can require the sponsor to carry out post-marketing studies to confirm the drug does in fact produce a clinical benefit such as increased survival.

Early access programs exist to allow people with life-threatening conditions to begin using promising new therapies **before** the FDA has formally approved them. Examples are the **treatment IND** program and the **parallel track program** that were designed specifically for individuals with AIDS whose condition prevented them from participating in clinical trials. Under these early access programs, individuals can receive investigational drugs that have shown in preliminary studies to be potentially useful. Once again, patients are informed and understand that they are accepting some of the risk when taking products that have not yet received FDA approval, but seriously ill patients are typically willing to accept more risk.

Slide 17 Once the clinical trials are completed the results are tabulated and analyzed. The sponsor submits to the Center a New Drug Application, or NDA, or a BLA, a Biologics License Application.

The application presents to FDA reviewers the entire history or "whole story" of the drug product from animal studies to human studies, manufacturing, to labeling. One thing that is not required in the application is the cost of the drug product. FDA has no authority over pricing. Our job is to review the data and determine if the product meets the criteria for marketing in the United States.

Slide 18 gives you an idea of how much paper a typical drug application contains! Traditional paper applications often run into the hundreds of thousands of pages and are delivered to the agency in tractor-trailers. As you can imagine, we are simply running out of warehouse space for all this paper.

Slide 19 The FDA views information technology as a strategic tool that can be used by the staff to accomplish their goals and objectives with greater efficiency and effectiveness. As a result, the FDA has been accepting portions of applications in electronic format for

several years and now we accept entire applications electronically. This means less paperwork for everyone, and quicker, more accurate reviews. You can see on this slide the dramatic difference in space from the previous one.

Earlier I showed you an organizational chart for CDER. The left arm showed the Office of New Drugs where there were six offices of drug evaluation. On **Slide 20**, the six offices are across the top and you can see that within each office there are several review divisions.

FDA is always looking for ways to carry out its public health mission more effectively. The agency sometimes changes its organization to strengthen the way it reviews products. Visit our website for the most current organization chart.

The applications final destination in CDER is determined primarily by the therapeutic indication for which it has been studied. So, for example, if the NDA is for a drug used to treat asthma, then the NDA will go to the second office of drug evaluation to the pulmonary division.

Before the members of CDER's review team apply their scientific technical expertise to the review of the application, they will decide if the application gets a priority review or a standard review. This classification determines the review time frame.

A priority review is for a drug that appears to represent an advance over available therapy, whereas, a standard review is for a drug that appears to have therapeutic qualities similar to those of an already marketed product.

Slide 21 The agency's mission depends more than ever on experienced physicians, toxicologists, chemists, statisticians, mathematicians, and other highly qualified and dedicated professionals. Their expertise is essential for making FDA's regulatory decisions balanced and fair, and for keeping the agency on the cutting edge of the technology and sciences used in medicine. Each division has several review teams. Most of the listed scientists exist on each team, but the type of application being reviewed dictates which technical experts are needed.

The project manager is responsible for the overall management of the application. He or she makes sure everyone is aware of deadlines, meeting times, and obligations. The project manager also acts as a source of contact between reviewers and the sponsor for any questions or clarification during the review process.

The medical officer, a physician, evaluates the results of the clinical tests, including adverse events.

Chemists evaluate methods of manufacturing controls, stability, and packaging. They ensure that the compound is stable and reproducible.

Statisticians evaluate design of study and validity of statistical analyses, and provide the physicians with a better idea of the power of the findings that are to be extrapolated to the patient population.

A Pharmacologist evaluates the animal testing in short- and long-term trials and relates the results to the potential effects in humans.

The establishment/facility reviewer inspects the manufacturing facilities

This team is responsible for reaching a decision regarding approval of the product. The team is basically trying to answer two questions:

1. Do the results of the well-controlled studies provide substantial evidence of **effectiveness**?
2. Do the results show the product is **safe** under the conditions of use proposed in the labeling?

It is important to remember that NO drug is absolutely safe--there's always a risk of an adverse event. We look at the population that would be using the drug and ask, "do the benefits to this population outweigh the risks?" If yes, we go ahead and approve the drug.

Slide 22 Sometimes, the Center or sponsor requests that an advisory committee review the product. This outside advice is sought so that the FDA will have the benefit of wider national expert input.

Committee members are scientific experts such as physicians, statisticians, pharmacologists, epidemiologists, as well as representatives of the public. The charter of each of the advisory committees provides for at least one member to represent the consumer or patient perspective. Consumer representatives make a valuable contribution by raising consumer concerns that might not be otherwise addressed before products come to the marketplace.

There are 18 standing advisory committees which weigh available evidence and provide scientific and medical advice on the safety, effectiveness, and appropriate use of products. Although advisory committees have a prominent role in the product approval stage, they are sometimes used earlier in the product development cycle and are sometimes invited to consider postmarketing issues.

The Center usually agrees with the advisory committee decisions, but they are **not** binding. To find out more about meeting dates, agendas, or obtain transcripts you can visit the FDA Advisory Committee web site link on our course page.

These open and public meetings allow the public to stay informed of trends in health care. They also work to enhance and increase the public's awareness of public health issues.

I will now turn the presentation over to Mary Kremzner who will share with you some more significant FDA regulations and strategic initiatives as well as the FDA's post-

marketing surveillance system, and finally the generic and over-the-counter drug review process.

Slide 23 Hi, and thanks for staying with us. As you have just finished learning about FDA's approach to drug review, it is clear that it has been well thought-out, well organized, and continually reviewed for areas in which we can improve. This approach to drug review at FDA began in the 1980s when there was a push to speed up the drug review process. FDA, working in concert with Congress and the drug industry, created the Prescription Drug User Fee Act of 1992. (This is another significant law illustrated earlier on our FDA timeline tree.)

PDUFA, as it is called, established a system whereby prescription drug manufacturers pay fees to have their new drug and biologic drug applications reviewed by FDA. This system provided the much-needed funds to implement a number of significant procedural changes to help speed the review of applications by, for example, hiring additional reviewers and obtaining information technology resources.

PDUFA also created a system that was more transparent to industry and provided review goal dates like those mentioned earlier (Standard and Priority reviews), meeting times with industry, more guidance documents, and more opportunity to work collaboratively. PDUFA was to sunset or end after 5 years. However, due to its overwhelming success, Congress chose to renew PDUFA two more times so we are now in PDUFA III which reauthorizes user fees through FY 2007.

You can find more information on PDUFA and the fee amounts at the website www.fda.gov/cder/pdufa.

Slide 24 Here again is the timeline of drug development. As explained earlier, the NDA review team takes an action on the NDA after their review is complete. There are three possible actions taken by the review team:

1. Approved – This indicates to the company that they may now market in the United States.
2. Not approved –tells the company that the product may not be marketed in the United States and with a detailed explanation as to why. Or,
3. Approvable –which indicates that FDA is prepared to approve the application upon the satisfaction of conditions specified in the complete response letter. These drug products may not be legally marketed until the firm has satisfied the identified deficiencies, as well as any other requirements that may be imposed by the FDA.

Approval is important. If the FDA approves a new drug, the drug product is now available to the American people. The drug also enters what we call the post-marketing

surveillance phase, which encompasses the lifetime of the product on the market. The FDA continues to monitor all drugs that are on the market throughout their lifetime.

It is important to keep in mind that it is impossible to detect all potential problems during clinical trials because they are of short duration and narrow populations. In response, the FDA has created several programs to address the continued monitoring for the safety of marketed drug products. Even with the best available data, products are sometimes found to have side effects that were not predictable or detectable in any clinical trials and other studies prior to product use in real-world conditions.

Slide 25 Post-Market Surveillance is an ongoing practice. CDER evaluates the safety profiles of drugs available to the American consumers using a variety of tools and disciplines throughout the life cycle of a drug. We maintain a system of post-marketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug development process.

Slide 26 gives a general organizational structure of the Office of Drug Safety's (ODS) three divisions. ODS is involved in many Center initiatives dealing with risk management.

The Office of Drug Safety works to reduce manageable medication risks by activities such as:

- issuing public health advisories,
- having proprietary trade name review committees made up of CDER health care professionals testing for confusing product names
- and, of course, FDA research and surveillance

Slide 27 Our MedWatch office is in the Office of Drug Safety . Adverse drug experience reporting is a vital link in ensuring that drugs on the market remain safe and effective. The most widely known monitoring system for reporting adverse events or product problems for marketed drug products, biologics, and devices is MedWatch. The web address for MedWatch is www.fda.gov/medwatch.

The FDA's MedWatch Reporting Program is designed to offer a spontaneous method for reporting adverse events and problems to FDA and then to use this information to educate health professionals about the critical importance of being aware of, monitoring for, and reporting adverse events and problems to FDA and/or the manufacturer.

Reporting adverse events to MedWatch is a voluntary program for health care practitioners and patients. Conversely, reporting is mandatory for the drug industry.

Whether the drug is on the market 10 days or 10 years, new information that impacts its clinical use can still be detected. Safety is a continually evolving process. That brings us to our outreach effort in MedWatch. The purpose of the MedWatch program is to enhance the effectiveness of post-market surveillance of medical products as they are

used in clinical practice and to rapidly identify significant health hazards associated with these products, and to ensure that new safety information is rapidly communicated to the medical community, thereby improving patient care. The MedWatch program is supported by over 140 organizations, representing health professionals and industry, that have signed on as MedWatch Partners to help achieve these goals. Our MedWatch staff is continuously working with our partners to develop ways to improve the flow of information across systems, and to find new ways to inform doctors, nurses, pharmacists, and patients about the safety of FDA-regulated products.

Slide 28 To aid in our constant post-marketing review of adverse events, we use the Adverse Event Reporting System, known as AERS. This is the database into which all adverse events are entered.

It can accept electronic submission of reports and even those from outside the United States and improves the quality of adverse event reports by incorporating internationally recognized standardized terminology.

Using this software and specialized training provides the Office of Drug Safety with the tools they need to triage, review the data, and assess risk. The reports are received from MedWatch, processed by the triage unit, and are available for on-line viewing by risk assessors. Risk assessors will receive reports based on primary surveillance criteria maintained within AERS. Risk assessors may view the data base or image view of a report on-line.

A promising new technology to enhance our monitoring capability is a technique called “data mining.” We use this technique for extracting meaningful, organized information from large complex databases. Data collected from suspected drug-related adverse events reports and other electronic medical information could aid in identifying signals of adverse events and the patterns in which they occur. The agency can then communicate this knowledge sooner to medical professionals and patients, thereby preventing more adverse events.

For example, if FDA risk assessors discover information not already identified in the product labeling that health care practitioners need to know, we can take action.

Slide 29 illustrates potential regulatory actions for post-marketing safety issues. The action FDA takes can be in several forms. For instance, sometimes the action is to add more information to the package insert or to have the company send a letter to health care practitioners alerting them to the new information. Or, it may be both. Each situation is addressed case by case by the staff.

Slide 30 Risk assessment is a continuous process for CDER. Throughout the drug development and after, we continue to assess if the benefit of a drug still outweighs any risk that may be associated with taking the drug. FDA continues to improve the methods by which we obtain and assess post-marketing information related to adverse events.

Traditionally, FDA was focused on pre-market approval and the quality of product but our role is now evolving. Patients believe that the "FDA seal of approval" means no risk when in fact every product has risks. Everyone (FDA, healthcare provider, and patient) has to be involved in this process and we have to communicate the benefit/risk ratio more effectively.

A good example of this is when FDA has had to remove some relatively safe products from the market because they weren't being used as labeled. This led to serious adverse events and sometimes-even death.

Examples such as this are rare, but it is another reason why the FDA is committed to providing accurate, science-based information on the risks and benefits of the product we regulate to all those who use them.

During the summer of 2003, the agency held a public workshop to present our thoughts on risk management and solicit views, and stimulate discussion from the public. The agency relies upon a national and global network of health, regulatory, and science partners, as well as industry representatives and other stakeholders. The FDA knows that productive relationships with its partners to plan, implement, and evaluate our risk management strategies is vital. By working closely with partners in risk management, the FDA's ability to closely manage the risk associated with the products FDA regulates is greatly improved.

Slide 31 shows yet another not so obvious, yet very effective, risk management technique. The responsibilities of the Division of Drug Marketing, Advertising and Communications, or DDMAC, include monitoring all advertising and promotion of marketed prescription drug products. Although the division is involved in research, writing guidance for industry and other activities, it is best known for its role in regulating advertising of prescription drug products.

Advertising directed to consumers must meet the same requirements as promotion directed to health professionals. Direct-to-Consumer advertisements are often printed in popular magazines and journals that are read by a broad audience. Reviewers evaluate whether the materials meet the requirements for advertising or promotional labeling.

DTC advertising of drugs has become an important source of patient information about prescription drugs. It is DDMAC's job to make sure that all advertising to consumers is fair, balanced, and provides adequate information.

For such advertising to best inform consumers, it must effectively communicate not just the potential benefits of the advertised prescription drug, but also potential risks such as those associated with drug interactions and the specific health condition of the individual considering taking the drug.

Considerable research suggests that DTC advertising helps people who have untreated conditions get the treatment they need, and encourages consumers to get more involved in understanding their health problems, both of which improve health outcomes.

DDMAC reviewers work closely with medical review staff when evaluating scientific claims used in promotional materials and contact the medical staff regarding scientific questions about products. Drug application reviewers may also send direct-to-consumer advertising pieces to the DDMAC consultant to ensure consistency in applying the regulations to this type of advertising.

As we continue our discussion on post-market surveillance and risk management, **Slide 32** demonstrates yet another method by which we continue to monitor drugs on the market. It is through our Office of Compliance. CDER employees work closely with field investigators to assure product quality and uniformity throughout the lifetime of each approved drug product. Compliance officers work with industry to address product recalls and drug shortage situations. They also serve as the focal point for compliance issues involving the import and export of pharmaceutical products.

As FDA is addressing new threats in the 21st century, our compliance officers' roles have expanded to include new activities investigating threats to public health that involve counterfeit drugs, internet health fraud, drug diversion and other illegal activities.

With a clearer understanding of drug development, post-market surveillance methods, and how we address risk assessment, let's move ahead. On the next few slides I want to explain in brief several Acts or statutes which Congress passed that we identified earlier in the presentation on our "oak tree" time-line.

Slide 33 In 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (the 1984 Amendments). This Act was passed to expedite the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of trade-name drugs without repeating the clinical trials. This was the first time Congress passed a law which had more of an economic impact rather than health impact. We define a generic drug as "a drug product that is comparable to a pioneer reference listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use."

As described earlier, reviewing a new drug application, or NDA, is complex. The approval process for generics is significantly less complex because there is no need to repeat the three phases of clinical trials. Instead of submitting a NDA for FDA review, a sponsor will submit an Abbreviated NDA, or ANDA.

For ANDA reviews, the sponsor must prove therapeutic equivalence, in other words, bioequivalence and pharmaceutical equivalence to the trade name drug. The generic drug product must act the same way in the blood as the originator's product and it must produce the same beneficial effects.

Slide 34 provides the definition of bioequivalence:

- The rate and extent of absorption do not show a significant difference from the listed drug
- The extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant

In other words, a generic drug may be marketed:

1. after patent and exclusivity protection ends or the patent owner waives its rights and
2. the company meets FDA requirements.

Slide 35 As part of the 1984 Amendments, FDA began to make publicly available a list of approved drug products. The publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (better known as the Orange Book), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration under the Federal Food, Drug, and Cosmetic Act. The main criterion for inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons.

The Orange Book contains therapeutic equivalence evaluations for approved multi-source prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. You may find out more about the Orange Book at the website link on the course page.

Slide 36 Another Act passed in the early eighties enabled FDA to promote research and marketing of drugs needed for treating rare diseases. This is called the Orphan Drug Act. Congress felt there was reason to believe that some promising orphan drugs would not be developed unless changes were made in the Federal laws to reduce the costs of developing such drugs, to provide financial incentives to develop such drugs; and it is in the public interest to provide such changes and incentives for the development of orphan drugs.

An "orphan" disease is a condition affecting fewer than 200,000 people in the United States, for example, Tourette's syndrome, or cystic fibrosis. Drugs for these diseases and conditions are commonly referred to as "orphan drugs." Before the Orphan Drug Act was passed in 1983, there were only 10 orphan drugs on the market. Now over 200 drugs and biological products for rare diseases have been brought to market since 1983.

This law has had a tremendously positive impact on the health of those Americans afflicted with rare diseases. To find out more about orphan drugs, you may visit the FDA website at www.fda.gov/orphan.

Slide 37 illustrates how the drug development process along with most other industries has become increasingly more global in approach. Research performed in one country may be used in other countries, where experience gained cycles back to all countries.

This unique project which began in 1990 brings together the regulatory authorities of Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. It is an agreement to take action on harmonization by participating in the **International Conference on Harmonization**, or ICH.

The goal is to make recommendations on ways to reduce the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonization is a more economical use of human, animal, and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health. To date, officials have met several times and agreed upon over 30 written guidance documents to promote harmonization.

The FDA and our partners in this project firmly believe that greater harmonization of international scientific standards on drug product quality will promote technological innovation for enhancing global public health protection.

Let's summarize briefly before we begin one last area of drug development, which focuses on over-the-counter drugs. We explained the new drug development process where a sponsor discovers a new drug, performs clinical trials, and submits an application to the FDA. Then we explained several key statutes, or Acts as we call them, which have helped shape the process, create incentives for research, and contribute to globalization. The outcome of all this is a FDA approved drug, which results in another prescription drug on the market to benefit the health of Americans. In fact, most drug approvals by FDA are for prescription drugs for reasons we will now explore.

On Slide 38, you see three mechanisms for an OTC drug product to be marketed.

The first method of developing and marketing an OTC drug is the process you learned today in which a company can perform all the research, clinical trials, etc., and submit a NDA for an OTC drug.

The second mechanism is the **prescription to OTC switch**. You see this typically on the pharmacy shelf, where your formerly "*prescription only*" drug is now available as a reduced strength over-the-counter version. This process occurs when the sponsor of the prescription drug NDA submits to FDA a supplemental application to "switch" status from prescription to over-the-counter.

The FDA reviews these applications carefully. Toxicity is a major issue in deciding whether to switch a drug from prescription to OTC status. Since almost any drug, if misused, can have serious side effects, FDA considers the drug's overall safety.

Another consideration in deciding whether or not a drug should be available without a prescription is whether the condition being treated can be self-diagnosed and recognized without the help of a health care practitioner. Not being able to self-diagnose a medical condition does not automatically prevent a product from switching to OTC status; FDA evaluates each drug on an individual basis.

The third mechanism is the **OTC drug review process**. This is a way in which products are marketed without the typical application process as described in the first two mechanisms.

Slide 39 In the OTC drug review process, FDA reviews the active ingredients in a product to ensure that they are safe and effective for OTC use.

To do this, the Center developed a review process for OTC products whereby an advisory panel of experts and scientists, review the safety and effectiveness of ingredients rather than specific products. The outcome of this review of ingredients was an OTC Monograph. A monograph is best described as a guideline that sets certain standards specifying ingredients, dosage, indications for use, and certain labeling.

The panel classifies ingredients into three categories.

I - meaning the ingredient is safe and effective;

II – the ingredient is unsafe and/or ineffective; and

category III – there is not enough data with which to make a decision.

The FDA reviews the panel's findings and publishes the results in the *Federal Register* as the Announced Notice of Public Rulemaking, or ANPR, for comment, suggestions, and recommendations from all interested parties. After the comment period ends, the FDA reviews and addresses the comments.

Slide 40 Based upon the comments and data submitted, FDA then publishes the proposed rule or Tentative Final Monograph, which is open again for the public to comment, submit data, make suggestions, and recommendations.

After this second comment period closes, the agency reviews and addresses all comments received and publishes a final rule or Final Monograph in the *Federal Register*. Once the final rule has been published, it becomes official and is codified in the Code of Federal Regulations, which contains all the regulations governing drug manufacturing. You can find the OTC *Federal Register* publications at the link on our course page.

At the point at which there is a Final Rule, any ingredient in category II (the unsafe and or ineffective designation) must be removed from the market.

This process takes months, and sometimes longer.

Slide 41 illustrates the new OTC label.

One commonality all OTC drug products have begun to share is the format for product labels. The FDA continues to help consumers make better-informed decisions about how to use their health care dollars. We know that consumers want the best information available about each of the products they use. And research has demonstrated that more and better information helps consumers make smarter and better informed decisions. This is best illustrated with the new OTC label.

As more consumers engage in self-diagnosis and self-medication, the FDA believes that consumers need quality information on the drugs they take. The new labeling rules makes choosing an OTC drug product a lot safer and easier for many Americans. Benefits include:

- Easier to read
- Standardized format and font
- Enable better product comparisons
- Ensure safe and effective usage

The success of the new OTC label was a collaborative effort that included industry, consumers, professional organizations and others.

Slide 42 With the advent of internet pharmacy where a consumer can buy over-the-counter and prescription drugs, there is not always a pharmacist to speak with when making choices regarding drug selection.

Since 1996, the FDA has been committed to using the Internet as means to help consumers, patients, health care professionals and others get access to the latest and best information on the risks and benefits of the products we regulate. From tips on how to buy drugs on-line from reputable pharmacies to our campaign to educate consumers about the pitfalls of drug importation, our goal is to improve and expand the use of information technology for reporting and tracking of drug-related information and new efforts to take action against modern snake-oil salesman who threaten the public with false hopes of misleading information.

On a more serious note, the events of September 11, 2001, and the subsequent anthrax attacks reinforced the need to enhance the security of the United States. As you will see on **Slide 43**, Congress responded by passing the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (the Bioterrorism Act). The FDA is now engaged in an accelerated, major new focus on helping develop and make available better countermeasures of biological, chemical and radiological attacks. We have already taken major steps to make available safe and effective treatments for certain nerve gases and radiological agents, and enhanced our stockpiles of treatments for other possible threats of biowarfare.

In fact, these events have compelled the FDA to refocus and incorporate enhanced security and safety measures. As the opportunities for developing better countermeasures

improve, FDA will be critically important in making these products available to the American people.

Slide 44 Our approach for countering the terrorist threat through drug development and review involves working with industry to develop medical countermeasures using state-of-the-art science, collaborating with other responding agencies and organizations, strengthening our own preparedness and response capabilities and remaining vigilant against potential threats to our Nation's health.

Slide 45 This concludes our presentation of the drug review process in the Food and Drug Administration Center for Drug Evaluation and Research. To view the mechanisms by which drugs are approved as a refresher to today's presentation or to augment our presentation, visit the CDER web site.

Slide 46 If you have questions or would like more information on any topic related to drug regulation, please visit our website at the Division of Drug Information, or you may call us at 888-INFO-FDA, or send an email to Druginfo@cder.fda.gov. This concludes our presentation. At this time, to receive continuing education credits, please complete your on-line self-assessment quiz and evaluation. Thank you.