FDA's Role in Public Health: Drug Efficacy, Safety, Quality, and Beyond

Course Introduction and FDA Overview

Course Welcome

Welcome to the U.S. Food and Drug Administration course on FDA's Role in Public Health: Drug Efficacy, Safety, Quality, and Beyond.

The mission of the FDA Center for Drug Evaluation and Research, or CDER, is to protect and promote public health by ensuring that patients have access to drugs that are safe and effective for their intended use and meet established quality standards. As you will learn, there is an immense, ever evolving, and complex public health responsibility associated with this mission.

Overview of FDA Human Drug Regulation

This course explains how U.S. public health policy has influenced and shaped the FDA protections that Americans have come to expect; provides an overview of CDER's role in the regulation of new drug development, marketed drugs, quality testing, and post-market surveillance; and highlights new methods, processes, and changes for human drug regulation in the United States.

Overall Learning Objectives

Upon completion of this course, you will be able to fulfill the following learning objectives:

- Describe and explain the drug development and assessment process in the United States for new drugs, therapeutic biological products, generic drugs, biosimilars, and over-the-counter (OTC) drugs.
- Outline CDER's role in post-marketing safety surveillance for medical products.
- Identify ways CDER disseminates safety information to both health care professionals and their patients.
- Describe CDER initiatives and commitments for the protection of public health.

FDA Overview

CDER is one of the six product centers. Each is responsible for overseeing the safety, effectiveness, and quality of various products, including medical devices, foods, veterinary medicines, biological products, and tobacco products.

In addition to the six product centers, the Agency also comprises the Office of the Commissioner, Office of Regulatory Affairs (field staff), the National Center for Toxicological Research, and more.

Center for Veterinary Medicine (CVM)

Center for Food Safety and Applied Nutrition (CFSAN)

Center for Biologics Evaluation and Research (CBER)

Center for Drug Evaluation and Research (CDER)

Center for Devices and Radiological Health (CDRH)

Center for Tobacco Products (CTP)

Oncology Center for Excellence (OCE)

Legislative Timeline

Before moving forward into the current state of human drug regulation, let's look back and highlight some of the Agency's significant legislative milestones. With the passage of the 1906 Pure Food and Drugs Act, FDA began as a small operation directed to address the problem of drug impurity and misbranding in the U.S. marketplace. Since 1906, Congress has passed many additional laws that have improved protections and public health for the American people. Below is an interactive timeline illustrating some of the significant landmarks and legislative actions that have occurred over the years and how FDA's consumer protection responsibilities have grown.

1906 Pure Food and Drugs Act: Prohibited interstate commerce in misbranded and adulterated food and drug products.

1930: Under an agricultural appropriations act, the Agency is named the Food and Drug Administration.

1938 Federal Food, Drug, and Cosmetic Act (FD&C Act): Replaced the 1906 Pure Food and Drug Act. Among other things, the FD&C Act required new drugs to be shown ***safe*** before marketing. This Act was passed in part in response to the 1937 public health disaster with Elixir of Sulfanilamide which received national attention. Elixir of Sulfanilamide was marketed without testing for safety (which at that time was not required by law). It contained the poisonous solvent diethylene glycol and as a result, over 100 people died, many of whom were children. FDA's efforts to broadcast the need for a new law to replace the 1906 Pure Food and Drugs Act is depicted in a traveling display called the "Chamber of Horrors."

1944 Public Health Service (PHS) Act: Incorporated the 1902 Biologics Control Act, serves as the legal basis for the requirement for licensing biologic products, and created the mechanism for gaining marketing approval of biological products that are regulated by CDER and CBER.

1962 Kefauver-Harris Drug Amendments: Added the requirement that drugs must also be proven ***effective*** for their intended use. FDA was now charged with ensuring that drugs available to the American public were not only safe but also effective. Also allowed FDA to set good manufacturing practices for industry and mandated regular inspections of production facilities.

1983 Orphan Drug Act: Passed by Congress to spur development of "orphan drugs," a term derived from the time when rare diseases were said to be forgotten or "orphaned" by the drug development industry. It promoted research and development of drugs and biological products for diseases that affect only small populations. By providing incentives to drug sponsors for developing orphan drugs, patient populations that were largely ignored by drug sponsors could now have new drugs available to treat their conditions.

The Rare Diseases Program works alongside the Office of Orphan Product Development, and supports people affected by rare diseases by accelerating, supporting, and facilitating the process of getting orphan drug products to market. A rare disease is one that specifically affects less than 200,000 people in the United States. But while the number of patients with any given rare disease may be small, the cumulative impact on public health is large. There are approximately 7,000 different rare diseases, collectively affecting as many as 30 million people or about 10 percent of the U.S. population.

1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments): Expedited the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand name drugs without repeating the research done to prove them safe and effective.

Generic drugs now account for 90% of prescriptions in the United States. From 2009-2018, competition from safe and effective generic drugs has saved the health care system about $2 trillion.

1987 Center for Drugs & Biologics Split: FDA's Center for Drugs and Biologics, created in 1982 by merging the Bureau of Drugs and the Bureau of Biologics, was split into CDER and the Center for Biologics Evaluation and Research, or CBER. This reorganization was necessary given the increasing number of new drug and biological product applications during this time and the backlog of reviews associated with these products.

1992 Prescription Drug User Fee Act (PDUFA) and Reauthorizations: Authorized FDA to collect fees for the review of human drug and biological products. Since the passage of PDUFA, user fees have played an important role in expediting the drug approval process.

PDUFA Fees help to support the following activities:

- Ensuring a sufficient scientific staff capacity for the drug assessment process
- Monitoring the safety of approved drugs and licensed biological products in the post-market setting
- Ensuring an up-to-date information technology infrastructure

Prior to PDUFA's enactment, FDA was understaffed, and drug assessment was slow and unpredictable.

PDUFA helps FDA to fulfill its mission of protecting the public health, while improving the predictability of assessment processes and accelerating innovation in the industry. Since the inception of PDUFA, FDA has dramatically reduced the assessment time for new drugs and biological products, without compromising the Agency's high standards for demonstration of safety, efficacy and quality of new drugs and biological products prior to approval.

Select *PDUFA* to learn about background legislation and user fee rates.

2007 FDA Amendments Act (FDAAA): Among other things, FDAAA expanded the authority of the FDA to assess and manage drug safety. It also created a foundation (Reagan-Udall) to modernize product development, accelerate innovation, and enhance product safety.

2010 Biologics Price Competition and Innovation Act of 2009 (BPCI Act): Amended the Public Health Service Act to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product.

2012 FDA Safety and Innovation Act (FDASIA): Among other things, FDASIA enacted the Generic Drug User Fee Amendments (GDUFA) and the Biosimilar User Fee Act of 2012 (BsUFA). These new programs built on PDUFA's successes in providing steady and reliable funding to maintain and support a staff of trained reviewers for generic and biosimilar drug products. Additionally, FDASIA provides FDA with new authorities to combat drug product shortages in the United States and to implement strategies to solicit the views of patients during the medical product development process.

Select each user fee link below to learn about background legislation and user fee rates:

- GDUFA
- BsUFA

2013 Drug Quality and Security Act (DQSA): Title I of DQSA, the Compounding Quality Act, made important updates to the FD&C Act related to the oversight of compounding human drugs. Title II of DQSA, the Drug Supply Chain Security Act, outlines critical steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. This will enhance FDA's ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful. The system will also improve detection and removal of potentially dangerous drugs from the drug supply chain to protect U.S. consumers.

2016 21st Century Cures Act: Designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.

2017 FDA Reauthorization Act of 2017 (FDARA): Amended the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for drugs, medical devices, generic drugs, biosimilar biological products, and other purposes.

2018 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act: Granted FDA additional authorities to advance its efforts to confront the opioid crisis.

2020 Coronavirus Aid, Relief, and Economic Security (CARES) Act: Grants FDA additional authorities intended to modernize the over-the-counter (OTC) drug development and review process that will help advance innovative, safe and effective options for consumers and secure a robust OTC marketplace. The law also provides the FDA with the authority to collect user fees from manufacturers of OTC monograph drugs. The new user fee program is referred to as the Over-the-Counter Monograph User Fee Program (OMUFA).

Regulations and Guidance Documents

Code of Federal Regulations (CFR): Drug regulations are codified in the Code of Federal Regulations, or CFR. These regulations are written in response to the laws passed by Congress. Title 21 of the CFR is made up of several volumes with both general and specific sections devoted to different FDA product areas (e.g., drugs, devices, and biological products). For example, regulations for drug products are mainly found in sections 200 and 300, while regulations for biological products are primarily in section 600. These regulations may be purchased in book/hardcopy form or viewed online.

Guidance Documents: Guidance documents describe FDA's interpretation of our policy on a regulatory issue (21 CFR 10.115(b)). These documents usually discuss more specific products or issues that relate to the design, production, labeling, promotion, manufacturing, and testing of regulated products. Guidance documents may also relate to the processing, content, and evaluation or approval of submissions as well as to inspection and enforcement policies. Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach can be used if the approach satisfies the requirements of the applicable statutes and regulations.

Guidance documents may be viewed or searched for online.

Summary

Some key points to remember:

- FDA comprises six product centers, including CDER, that are collectively responsible for overseeing the safety, effectiveness, and quality of various products, including, but not limited to medical devices, foods, veterinary medicines, biological products, and tobacco products.
- Congress regularly passes new legislation intended to strengthen drug development, expand access, and improve protections for the American people.
- CDER is a nimble organization that works to ensure that safe, effective, and high-quality drugs are available to improve the health of people in the United States.
- Drug regulations are codified in Title 21 of the Code of Federal Regulations, and guidance documents describe FDA's interpretation of our policy on regulatory issues.

Congratulations! You have successfully completed the course introduction, which provides an overview of over 100 years of history and evolution of FDA drug regulation!

Module 1: CDER Product Development and Assessment

Lesson 1: New Drug Development and Assessment

Introduction and Learning Objectives

CDER oversight of new drug development and assessment of drug and biologic applications will be explored in this lesson.

After completing this lesson, you should be able to:

- Describe the new drug development and assessment process.
- Describe the Prescription Drug User Fee Act (PDUFA) and its effect on drug review.
- Identify ways FDA facilitates access to investigational (unapproved) drug products.

Lesson 1: New Drug Development and Assessment

Before learning about the new drug development and assessment process, let's first learn more about the organizational structure and work force involved in product assessment.

The scientific review staff are organized into offices and divisions based on therapeutic area. Two examples of scientific review staff organization within the CDER Office of New Drugs are given below:

- Data on drug products indicated for the treatment of hypertension are reviewed by the Division of Cardiology and Nephrology.
- Data on drug products intended for the treatment of ulcerative colitis are reviewed by the Division of Gastroenterology.

Organizing the review staff in this manner helps to ensure that appropriate medical backgrounds and expertise are applied to Agency decision making.

Learn more about review divisions at the Web site for the Office of New Drugs.

Scientific Review Team Involved in Product Assessment

Each product application is assessed by a multi-disciplinary scientific review team with members from across CDER.

- The team members may include medical officers (physicians), pharmacologists, toxicologists, regulatory project managers, chemists, manufacturing process experts, microbiologists, pharmacologists, clinical pharmacologists, safety specialists, epidemiologists, statisticians, and facility inspectors.
- Scientific review teams use a collaborative approach to monitor their assigned drug products from the investigational phase (when the drug is first introduced to FDA) through the post-marketing phase (after a drug product is approved).

Other Key CDER Staff: Pharmaceutical Quality

Staff in the Office of Pharmaceutical Quality (OPQ) perform a scientific evaluation of drug product quality. The Office establishes quality standards for new drugs, generic drugs, biological products, biosimilar products, and nonprescription products across the product lifecycle. OPQ's team approach to quality assessment combines assessment of marketing applications with the evaluation of manufacturing facilities, leading to a single, more informed quality assessment.

OPQ is also responsible for drug testing, evaluating recalls data and adverse event reports to proactively identify risks to product quality and to mitigate quality issues, for example, before drug shortages occur.

Learn about pre-approval inspections on the next screen.

Learn more about OPQ's responsibilities at the Office of Pharmaceutical Quality's Web site.

Other Key CDER Staff: Pharmaceutical Quality - Pre-Approvals

OPQ staff are involved in determining when "pre-approval" inspections are needed for manufacturing facilities prior to approving drug applications. These inspections are designed to investigate whether drug products are of high quality, properly manufactured/labeled, safe, pure, and meet applicable drug approval requirements. Pre-approval inspections evaluate manufacturing sites where drug products might be produced for marketing, pending approval of drug applications. OPQ staff conduct some of these inspections and coordinate with Office of Regulatory Affairs (ORA) field investigators to conduct others. OPQ reviews the inspection findings and collaborates with all related offices in making a recommendation on the approvability of marketing applications.

Other Key CDER Staff: Bioresearch Monitoring (BIMO) Staff

FDA's Bioresearch Monitoring (BIMO) staff are responsible for a comprehensive program of on-site inspections related to clinical and preclinical studies and of data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research.

BIMO staff work to ensure the quality and integrity of data submitted to the agency in support of product approvals as well as to protect the rights and welfare of human subjects involved in FDA-regulated research.

Learn more about FDA's Bioresearch Monitoring program on BIMO's Web site.

The Drug Assessment Process

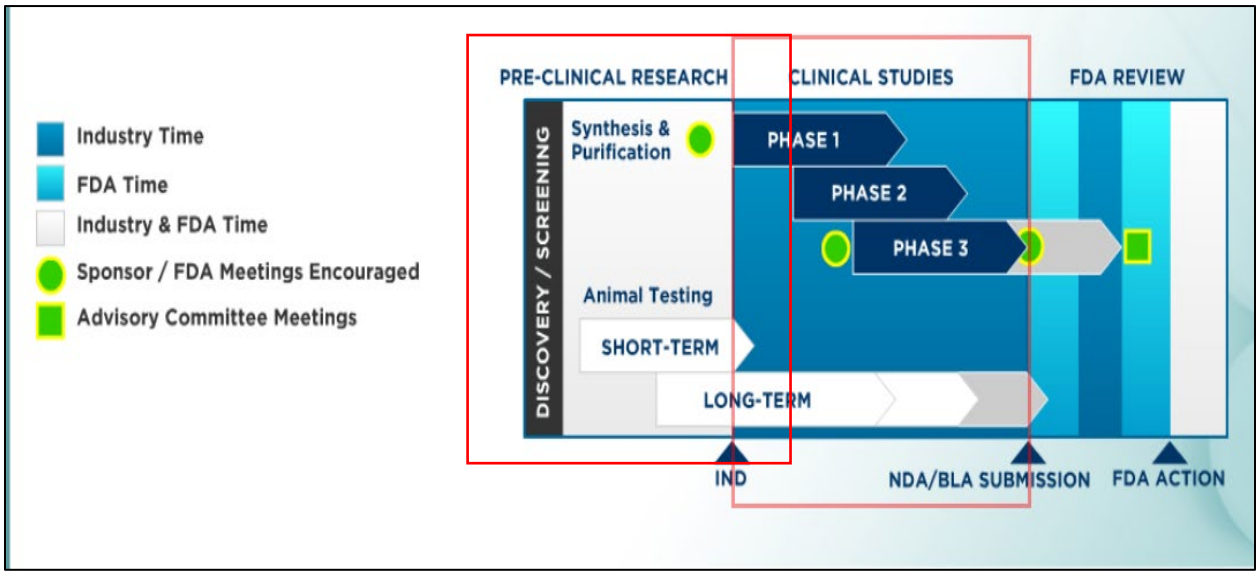
Now that we've covered the multi-disciplinary framework of the scientific review staff, you will learn how a new drug product moves through the process of development, assessment, and marketing in the United States.

Every drug approved by FDA must undergo rigorous scientific testing to ensure that it is safe and effective for its intended use.

The Agency reviews the conduct and results of non-clinical and clinical studies submitted by the sponsor and evaluates sponsor compliance with requirements for manufacturing the finished drug product.

The Drug Review/Assessment Process

This diagram illustrates the overall drug review process and will serve as a guide through this learning activity. It encompasses three stages: preclinical research, clinical studies, and FDA's assessment of the sponsor's application. Let's begin exploring the pre-clinical research phase.



Alternative Text: Chart displays the three phases of the Drug Review Process. The first phase is Pre-Clinical Research and includes discovery and screening, synthesis and purification and short-term animal testing. The second phase is Clinical Studies and includes three phases of studies and long-term animal testing. The third phase is FDA Review and includes NDA/BLA submission and FDA action. The first phase is highlighted on this page.

Preclinical Research: Discovery and Screening

Each sponsor works to develop a candidate product that possesses a desired therapeutic effect but is free of harmful effects. Out of several thousand molecules that may be screened by researchers, only very few will show promise as candidate products. Out of those few potential candidates, even less will complete the rigorous preclinical and clinical testing. In the end, very few candidate compounds actually make it to market.

There are several methods used to identify candidate compounds for research. One is computer modeling, allowing researchers to predict chemistry and speed up the discovery process. In some cases, computer modeling can test candidate products through simulations with virtual organs or patients.

Preclinical Research: Discovery and Screening, Cont.

Using a small-molecule drug as the example, once the sponsor has identified a candidate drug, preclinical testing can begin. During preclinical research, the sponsor studies the candidate drug's chemical properties to evaluate where it may have a desired pharmacological effect. The sponsor also develops steps for drug synthesis and purification, and conducts in vitro and in vivo analyses.

Short- and intermediate-term animal studies are also conducted during this phase. The goal of animal studies is to gather sufficient data to demonstrate that the candidate drug is reasonably safe before beginning clinical studies in humans. (Note that the process may be different for biological products, which are derived from living cells and more complex than small-molecule drugs.)

Preclinical Research: Animal Testing – Short-term

There are two types of **short-term animal studies** typically conducted during the preclinical research:

- **Pharmacokinetic (PK) studies** evaluate how the drug is processed by the body. This includes the absorption, distribution, metabolism, and excretion of a candidate drug and its metabolite(s).
- **Acute toxicity studies** evaluate toxicities that may immediately arise after a drug is administered. Genotoxicity (damage to DNA) and pharmacological effects on cardiovascular, central nervous, and pulmonary systems are also usually of interest. Short-term testing in animals can range from 2 weeks to 3 months, depending on the proposed use of the candidate drug.

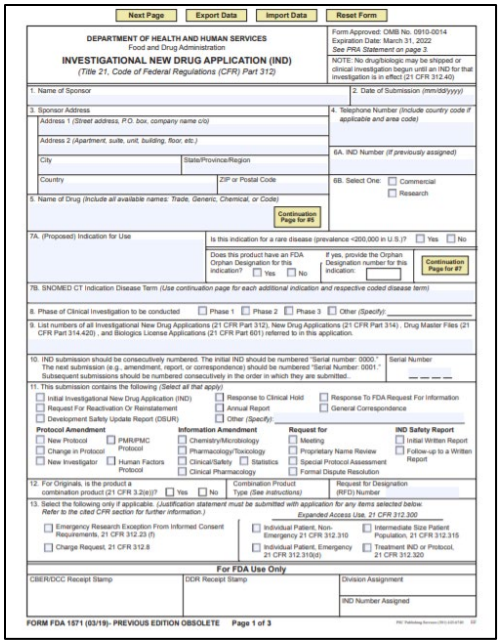
Investigational New Drug Application (IND)

After preclinical research has demonstrated the candidate drug to be reasonably safe and potentially therapeutic, the sponsor may request authorization from FDA to pursue clinical research (i.e., research in humans). This request is initiated with an investigational new drug application (IND), which presents all preclinical data.

Research proposed through an IND may begin 30 calendar days after FDA receives the IND (or on earlier notification by FDA), unless FDA issues a clinical hold, an order to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation.

CDER reviewers take this decision to initiate clinical studies covered by an IND very seriously, as human protection is of paramount importance to FDA. An IND must be reviewed by an institutional review board (IRB) and contain commitments to obtain informed consent from the research subjects.

FDA Form 1571, shown here, accompanies an IND submission for human subject research.



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
6A. IND Number (If previously assigned)
6B. Select One: Commercial Research
5. Name of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
7A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
7B. SNOMED CT Indication Disease Term (Use continuation page for each additional indication and respective coded disease term)
8. Phase of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify)
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following (Select all that apply)
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify)
Response To FDA Request For Information
General Correspondence
Protocol Amendment: New Protocol, Change in Protocol, New Investigator, PMR/PMC Protocol, Human Factors Protocol
Information Amendment: Chemistry/Microbiology, Pharmacology/Toxicology, Clinical/Safety, Statistics, Clinical Pharmacology
Request for: Meeting, Proprietary Name Review, Special Protocol Assessment, Formal Dispute Resolution
IND Safety Report: Initial Written Report, Follow-up to a Written Report
12. For Originals, is the product a combination product (21 CFR 3.2(e))? Yes No
Combination Product Type (See instructions)
Request for Designation (RFD) Number
13. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp
CDR Receipt Stamp
Division Assignment
IND Number Assigned

FORM FDA 1571 (03/19)- PREVIOUS EDITION OBSOLETE Page 1 of 3

Alternative Text: Example screengrab of Form 1571

Preclinical Research: Animal Testing – Long-term

Even after testing in humans begins, preclinical studies continue after the submission of an IND application. In fact, long-term animal testing may run from months to two years, potentially lasting throughout the clinical trial period.

Long-term animal studies often investigate chronic toxicity and carcinogenicity. In addition, after human testing begins, animal tests may be needed to investigate the potential to affect fertility, induce birth defects, or alter neonatal development.

Clinical Studies

Clinical trials are a critical tool for determining which drugs are safe and effective for human use.

Clinical Studies, Cont.

The complexity of drug development and the number of clinical trials have increased over time, as more sophisticated technologies have emerged and as our understanding of disease mechanisms has expanded in the new era of genomic medicine. The increase in complexity begins in exploratory testing and continues through clinical trial testing and to post-market use.

Agency staff need to continually evaluate the clinical trial system to ensure that it is functioning in parallel with emerging scientific and technical knowledge. A critical task is to make sure standards are in place to maximize the safety and protection of trial participants.

In clinical research, human studies generally take place under three phases. Watch a video on the FDA Web site which describes each of these three phases of new drug development.

Clinical Studies, Cont.

The approach to clinical trials has evolved considerably and continues to do so.

FDA has introduced modern and innovative concepts to the foundational clinical trial design and clinical outcome assessments, which will improve the development and assessment of novel medical products. FDA initiatives encourage the use of state-of-the-art innovations such as adaptive trials, modeling, and more.

FDA is also focused on the appropriate use of surrogate endpoints in individual drug and biological product development programs, and the Agency facilitates a public process to support biomarker qualification as a drug development tool.

In addition, the staff continue to elevate patient voices in developing new medical products to treat disease. Patient Focused Drug Development, beginning in 2012 as patient and advocate meetings under FDA auspices, has evolved to incorporate patient perspectives of specific disease states as a crucial element of FDA's decision-making process.

Drug Development Tools

Drug Development Tools (DDTs) are methods, materials, or measures that have the potential to facilitate drug development. Examples of DDTs may include:

- Biomarkers used for clinical trial enrichment
- Clinical outcome assessments (COAs) used to evaluate clinical benefit
- Animal models used for efficacy testing under the regulations commonly referred to as the Animal Rule

To support drug development efforts, FDA has established programs for formal qualification of each of these types of development tools, where a formal package is voluntarily submitted for evaluation and assessment by FDA staff. DDT Qualification Programs are currently available for biomarkers, COAs, and animal models for use under the Animal Rule.

Read more about DDTs by visiting the Drug Development Tool Programs and Initiatives Web site.

Real World Data and Real World Evidence

Another innovative aspect of facilitating drug development is the integration of real world data (RWD) and real world evidence (RWE) into regulatory decision making.

RWD are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-related activities in out-patient or in-home settings
- Health-monitoring devices

RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Real World Data and Real World Evidence, Cont.

The health care community has been using these data to support insurance coverage decisions and to develop guidelines and decision support tools for use in clinical practice. Medical product developers are

using RWD and RWE to inform clinical trial designs (e.g., large simple trials, pragmatic clinical trials) and observational studies to generate innovative, new treatment approaches.

With the development of sophisticated and new analytical capabilities, we may be better able to analyze RWD and apply those results to medical product development to support new indications for existing drugs.

Read more about RWE and RWD.

Expanded Access

There are many reasons for participating in clinical trials. In addition to contributing to medical knowledge, some people participate because there is no treatment available for their disease, treatments they tried have not worked, or they are not able to tolerate the current treatments.

FDA realizes that some patients may be unable to participate in a clinical trial. For patients with serious or immediately life-threatening diseases, the FDA is committed to facilitating access to investigational medicines while protecting patients and making sure that they are able to make informed decisions. FDA facilitates such access as a part of the Expanded Access program.

Expanded Access, Cont.

Sometimes called "compassionate use," expanded access is a potential pathway for a patient with **a serious or immediately life-threatening disease or condition to gain access to an investigational medical product** (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

FDA has a long history of facilitating expanded access to investigational drugs for use in patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives.

It is important to note that sponsors may choose, but are not required, to provide an investigational medical product in response to a request for expanded access.

Visit FDA's Web site on Expanded Access to learn more.

Expanded Access, Cont.

Under FDA's current regulations, there are three categories of expanded access.

Treatment IND or Protocol (for Large Patient Populations)

Treatment IND or Protocol permits an investigational drug to be used for widespread treatment. An IND is submitted for an investigational drug showing promise in clinical testing for a serious or immediately life-threatening condition while the final clinical work is being conducted and/or FDA assessment of the marketing application is taking place.

Intermediate-Size Patient Population IND or Protocol

FDA may permit an investigational drug to be used for the treatment of a patient population that is generally smaller than that typical of a treatment IND or treatment protocol (but more than an individual patient). FDA may ask a sponsor to consolidate expanded access under this type of expanded

access when the Agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

Individual Patient IND or Protocol (Non-Emergency) - When FDA determines an individual patient cannot obtain an investigational drug under another IND or protocol, a licensed physician may be permitted to use the investigational drug to treat the patient under expanded access.

Individual Patient IND or Protocol (Emergency) - In an emergency situation, the request to use an investigational drug to treat an individual patient may be made via telephone or other rapid means of communication, and authorization to use the drug may be given by the FDA official over the telephone. In these situations, known as emergency INDs or protocols, treatment with the investigational drug may begin prior to FDA's receipt of the written submission that is to follow the initial request.

Expanded Access, Cont.

More recently, Form 3926 was developed specifically for physicians seeking to treat an individual patient under expanded access. The form is faster and easier to complete than the traditional Form 1571.

Information on how to apply for expanded access is available at the following:

- Expanded Access: Information for Physicians Web page
- Expanded Access Navigator
- FDA's Guidance for Industry - Individual Patient Expanded Access Applications: Form FDA 3926
- FDA Drug Info Rounds Expanded Access Video Series

Visit the FDA Forms Web site to access forms used to submit an expanded access IND or protocol.

Expanded Access, Cont.

FDA's Project Facilitate is a call center, developed under the Oncology Center of Excellence, to assist oncology health care providers and regulatory professionals in navigating the process for requesting expanded access to treat individual patients with cancer.

Project Facilitate staff are equipped to provide step-by-step assistance with expanded access submissions geared towards community health care providers who may not have an internal regulatory support staff where they practice.

Project Facilitate staff, utilizing the Reagan-Udall navigator as a resource, will guide the caller to:

- IRB resource options
- Expanded access contact for the drug company
- Advice on necessary information to include in their submission
- Help with completing form FDA 3926, if needed

Expanded Access, Cont.

Project Facilitate also collects data concerning the provision and denial of drug/biologic access by manufacturers.

Project Facilitate staff follow up with the health care provider or their designee to remind them to submit the required summary report on whether the patient received benefit from treatment and if there were adverse events.

Health care providers and regulatory professionals may call Project Facilitate at (240) 402-0004 during regular business hours, 8 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, or email OncProjectFacilitate@fda.hhs.gov.

Patients and families with questions can call FDA's Division of Drug Information at 301-796-3400 or email druginfo@fda.hhs.gov.

Knowledge Check

Question 1

Which of the following initiates a request for authorization from FDA to pursue clinical research?

a) Application to market a new or abbreviated new drug or biologic for human use

b) Investigational new drug application (IND)

c) New animal drug application

d) Phosphatase test

Correct answer feedback: Correct! The correct answer is b. The investigational new drug application (IND) initiates a request for authorization from FDA to pursue clinical research.

Right To Try (RTT)

In 2018, Congress established an alternative pathway for patients diagnosed with life-threatening diseases or conditions to request, and for sponsors or manufacturers to choose to provide, access to certain unapproved, investigational drugs, including biological products. Under RTT, patients and their physicians work directly with sponsors and manufacturers to obtain access to certain investigational drugs. FDA's role in implementation of the RTT Act is largely limited to receipt of sponsors' and manufacturers' annual summaries and posting an annual report regarding RTT use.

Learn more about RTT.

FDA Application Assessment and Action

Upon completion of clinical studies, the results are tabulated and analyzed by the sponsor, who then submits a New Drug Application (NDA) or Biologics License Application (BLA) – also known as the marketing application - to the FDA to request marketing approval for their product in the United States.

FDA Application Assessment and Action: NDA/BLA Submission

The NDA or BLA provides a compendium of the entire history, or "whole story," of the drug product. The review team is responsible for evaluating the data independently and assessing the proposed labeling to determine if the product meets the safety and effectiveness standard for the proposed use(s) and marketing in the United States.

Knowledge Check

Question 2

Which of the three categories of expanded access allows for an investigational drug to be used for ***widespread*** treatment?

a) Treatment IND or protocol

b) Intermediate-size patient population IND or protocol

c) Individual patient IND or protocol

Correct answer feedback: Correct! The correct answer is a. Treatment IND or protocol permits an investigational drug to be used for widespread treatment. An IND is submitted for an investigational drug showing promise in clinical testing for a serious or immediately life-threatening condition while the final clinical work is being conducted and/or FDA assessment of the marketing application is taking place.

FDA Application Assessment and Action: Prescription Drug Product Labeling

Prescription drug labeling, which is proposed by the sponsor and reviewed and approved by the FDA, includes:

- Prescribing information
- FDA-approved patient labeling
- Carton and container labeling

The Prescribing Information provides a summary of the essential information needed to use a drug safely and effectively.

FDA-approved patient labeling includes:

- Instructions for Use (patient labeling for drugs that have complicated or detailed patient-use instructions including how to prepare, administer, handle, store, and/or dispose of a drug)
- Medication Guides (patient labeling required for certain drugs for safe and effective use)
- Patient Package Inserts (patient labeling required for oral contraceptives and drugs that contain estrogen)

FDA Application Assessment and Action: Prescription Drug Product Labeling, Cont.

FDA-approved prescription drug labeling is available on FDA's Drugs@FDA Web page. Furthermore, the most recent prescription drug labeling is available inn several resources, including National Institute of Health's DailyMed Web page as well as the FDALabel Web page. These Web sites provide information from prescription drug labeling free to consumers, health care professionals, and health care information professionals.

Select each image to access the respective Web site.

- Drugs@FDA
- DailyMed
- FDALabel

Download the Drugs@FDA Express Mobile App here.

FDA Application Assessment and Action: Prescribing Information – Format

Highlights of Prescribing Information (Highlights)

[Videos contain no audio narration; transcript unavailable]

Table of Contents (Contents)

[Videos contain no audio narration; transcript unavailable]

Full Prescribing Information (FPI)

[Videos contain no audio narration; transcript unavailable]

FDA Application Assessment and Action, Cont.

Sometimes during the assessment of an NDA/BLA, or at other times during a product's lifecycle, FDA will call upon an Advisory Committee for an expert opinion and/or recommendation on a topic. Advisory Committees are made up of scientists, physicians, and patient and consumer representatives who are not FDA employees.

The primary role of an Advisory Committee is to provide FDA with independent advice on marketing applications as well as on FDA policies. Advisory Committees contribute to the quality of Agency regulatory decision-making and lend credibility to the application assessment process. By listening to the advice of an Advisory Committee, FDA is better equipped to make sound decisions. However, it should be noted that Advisory Committee recommendations do not bind the Agency to any decision. Although their recommendations and advice are important to the FDA, the final regulatory decision must rest with the Agency.

FDA Application Assessment and Action, Cont.

Advisory Committees also convene to discuss post-marketing safety issues. Advisory Committee meetings generally are open to the public and often receive considerable media attention, which helps promote the transparency of FDA's decision-making process.

The calendar, briefing documents, and transcripts are all posted on the FDA Web page.

Expedited Programs for Serious Conditions

FDA has four principle programs to ensure that therapies for serious conditions are available as soon as an appropriate conclusion can be reached regarding product benefits and risks. Read more about the different types of expedited programs by selecting one of the boxes below:

Fast Track Designation

This designation is intended to facilitate the development and expedite the review of drugs to treat serious conditions to address an unmet medical need. The sponsor of a drug that receives fast track designation will typically have more frequent interactions with FDA during drug development; depending on circumstances, the sponsor may also be eligible for other expedited programs if relevant criteria are met. In addition, sponsors of products that have been designated as fast track are eligible to submit portions of their NDA or BLA before the entire application is complete, a process known as *rolling review*.

Accelerated Approval

This is a highly specialized program for speeding the development and approval of promising therapies that treat a serious condition and provide meaningful advantage over available therapies. If a drug is developed and reviewed under the accelerated approval pathway, CDER reviewers often base a determination of the product's safety and effectiveness on the drug's effect on "surrogate endpoints." A surrogate endpoint is a laboratory finding or physical sign that is reasonably likely to predict the drug's clinical benefit. For example, a drug may be approved under accelerated approval based on the shrinking of tumor size (the surrogate endpoint) rather than increased survival (the clinical benefit). Accelerated approval can also be granted on the basis of an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) and is reasonably likely to predict an effect on IMM.

For drugs and biological products approved under accelerated approval, the FDA requires applicants (as a condition of receiving accelerated approval) to conduct post-marketing confirmatory trials to verify and describe the drug's clinical benefit. If these confirmatory trials fail to verify the predicted clinical benefit, FDA may withdraw accelerated approval.

Breakthrough Therapy Designation

Breakthrough therapy designation is intended to expedite the development and review of drugs for serious conditions where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on a clinically significant endpoint. With this designation, the Agency will provide intensive guidance on an efficient drug development program and has an organizational commitment to involve senior management in such guidance. Additionally, a breakthrough therapy designation makes the drug development program eligible for rolling review, and other actions to expedite review may be taken if appropriate.

Priority Review Designation

Under PDUFA, FDA agrees to specific performance goals (deadlines) for completing the review and taking an action on a marketing application. Whereas the standard review time goal is set at 10 months, *priority review* is available for an application for a drug or biologic that is indicated for a serious condition and, if approved, would provide significant improvement in safety or effectiveness for a specific indication. The PDUFA performance goal for reviewing and acting on a *priority review* application is 6 months.

FDA Action

Upon conclusion of the assessment period, the review team recommends action on the marketing application. The Agency will accordingly take either of two possible actions for an NDA or BLA: "Complete Response" or "Approval."

FDA will send the applicant a complete response letter if the Agency determines that it cannot approve the application in its present form. The complete response letter will describe specific deficiencies and, when possible, outline recommended actions the applicant might take to better position the application for approval.

In contrast, if the drug or biological product has met Agency standards for quality, safety, and effectiveness for its intended use(s), FDA will issue an approval letter and the drug can then be

marketed in the United States. FDA's work continues as the product then enters the post-marketing surveillance phase.

Knowledge Check

Question 3

Which of the following are true about PDUFA?

a) It sets a 6 month goal for review of priority applications.

b) It sets a standard for intensive guidance on drug development programs for all applications.

c) It sets a standard review time for 10 months for priority review NDAs and BLAs.

d) It allows approval for all drug products based on a surrogate endpoint.

Correct answer feedback: Correct! The correct answer is a. PDUFA sets a 6 month goal for review of priority applications.

Lesson 1 Summary

Some key points to remember include:

- Sponsors submit marketing applications. FDA then assesses preclinical and clinical data to ensure that the drug product is safe and effective for its intended use.
- PDUFA authorizes FDA to collect user fees, which provide FDA with the necessary resources for the timely and predictable assessment of new therapies without compromising FDA's high standards.
- FDA has implemented mechanisms for patients to access unapproved or investigational drug products as well as intensive review programs that bring new products to market faster without compromising safety.

Congratulations! You have successfully completed this lesson!

Lesson 2: Regulation of Nonprescription Drugs, Generic Drugs, and Biosimilars

Now that you have a basic overview of the laws and regulations governing the new drug development process, lesson two introduces FDA’s regulation of nonprescription or over-the-counter (OTC) drug products, generic drug products, and biosimilars.

After you complete this lesson, you should be able to:

- Describe how nonprescription, generic, and biosimilar drug products are regulated.
- Explain key actions and legislation involved in the regulation of generic and biosimilar products.

Regulation of Nonprescription Drugs

There are over 100,000 marketed nonprescription or OTC drugs.

Nonprescription drugs must be safe and effective for use by the general public without the supervision of a health care professional.

Characteristics of nonprescription drugs include:

- Low misuse and abuse potential
- Condition to be treated is self-diagnosable
- Does not require a health care professional for safe and appropriate use
- Has adequate labeling so that consumers can self-diagnose, self-select, self-administer, and know when to stop using the drug

Self-selection is the decision a consumer makes to use or not to use a drug product based on reading the information on the drug product labeling and applying knowledge of his or her personal medical history.

Regulation of Nonprescription Drugs, Cont.

How does a new nonprescription, or over-the-counter (OTC), drug come to market? There are two regulatory pathways: **Drug Application (NDA/ANDA) Process** and **OTC Drug Review (OTC Monograph) Process.**

Drug Application Process

One possible pathway is through approval of a new drug application (NDA) or abbreviated new drug application (ANDA). The process for reviewing and approving an NDA or ANDA for a nonprescription or OTC drug is in many ways similar to the process for a prescription drug. Visit the FDA Web site for more information.

Prescription-to-Nonprescription Switch

In some instances, drugs that were initially approved under an application only for use under supervision of a health care professional (that is "prescription only" or Rx) can be approved for nonprescription use. This is sometimes referred to as a prescription-to-nonprescription or Rx-to-OTC switch. In these cases, the application holder for the prescription drug submits data to CDER to demonstrate that the drug can be safely self-selected and used by the consumer without supervision of a health care professional. Such applications often contain consumer behavior studies to demonstrate that consumers can read the product label and understand how to use the product safely without the supervision of a health care professional.

FDA maintains a list of drugs that have been switched from prescription to nonprescription status.

Direct to Nonprescription

Sometimes new drugs are developed specifically for introduction as nonprescription products, never having previously been approved as prescription only.

Regulation of Nonprescription Drugs, Cont.

How does a new nonprescription, or over-the-counter (OTC), drug come to market? There are two regulatory pathways: **Drug Application (NDA/ANDA) Process** and **OTC Drug Review (OTC Monograph) Process.**

OTC Drug Review (OTC Monograph) Process

The most common regulatory pathway to market for OTC drugs is the OTC monograph system (“OTC Drug Review”). The OTC Drug Review establishes regulatory monographs that describe the conditions

under which OTC products are considered to be generally recognized as safe and effective (GRASE) for various therapeutic categories, such as analgesics, cough and cold, and sunscreens. OTC drug monographs are a kind of "rulebook" covering acceptable active ingredients, doses, formulations, labelling, and testing. A drug that is marketed consistent with the conditions set forth under a final monograph and all other applicable OTC requirements is considered generally recognized as safe and effective for the uses set forth under the monograph and does not require FDA approval prior to marketing. On the other hand, if an OTC drug does not conform to an OTC monograph or is not otherwise covered under the OTC monograph system, it will require FDA approval through the application process.

OTC Monograph Reform

On March 27, 2020, the President signed into law H.R. 748, the “Coronavirus Aid, Relief, and Economic Security Act” (CARES Act). The CARES Act includes an important legislative initiative that reforms and modernizes the way OTC monograph drugs are regulated in the United States.

The CARES Act amends the FD&C Act to:

- Modernize the OTC drug review and OTC monograph drug development process
- Provide FDA with the authority to collect user fees dedicated to OTC monograph drug activities

Over-the-Counter Monograph User Fee Act

The new user fee program, which we refer to as the Over-the-Counter Monograph User Fee Act (or "OMUFA"), is modeled after the successful Prescription Drug User Fee Act (PDUFA). For OMUFA purposes, industry-paid fees will help fund a portion of FDA’s regulatory activities for OTC monograph drugs and FDA agreed to adhere to performance goals, including to review submissions within specific time frames. FDA anticipates that this user fee program will provide additional resources to help the agency conduct these important regulatory activities in a timely manner and ultimately help provide the public with access to innovative OTC monograph drugs.

Find additional information on the OMUFA webpage.

Innovative Approaches for Nonprescription Drugs

FDA has issued a draft guidance titled "Innovative Approaches for Nonprescription Drug Products." The draft guidance describes two innovative approaches that may be useful to consider for demonstrating safety and effectiveness for a nonprescription drug product in cases where the drug facts labeling alone is not sufficient to ensure that the drug product can be used safely and effectively in a nonprescription setting.

FDA believes the innovative approaches described in this guidance could lead to the approval of a wider range of nonprescription drug products, including drug products that may treat chronic conditions or other conditions for which the limitations of the drug facts label (DFL) present challenges for adequate communication of information needed for safe and effective use without the supervision of a health care practitioner.

Approval of Generic Drugs: Office of Generic Drugs

The approval process for generic drug products requires the introduction of the Office of Generic Drugs (OGD), which employs several hundred highly skilled scientists, health care, and regulatory professionals who work to ensure that generic drug products are of high quality, possess the same performance characteristics as their respective brand-name reference products, and are as safe and effective as their respective brand-name reference products.

Bioresearch Monitoring (BIMO) staff in the Office of Compliance (OC) and Office of Translational Science (OTS) are also involved in the development of generic drugs, through the inspection and evaluation of the conduct and regulatory compliance of clinical and analytical bioequivalence studies submitted under ANDAs.

Approval of Generic Drugs: Abbreviated New Drug Application

For a sponsor to market its generic drug, it must first submit an application to FDA, called an ANDA.

FDA requires drug companies to demonstrate that a proposed generic drug is the same as the brand-name drug that it copies. The ANDA submitted by drug companies must show the generic drug to be the same as the brand-name drug in the following ways:

- The active ingredient(s) in the generic drug is the same as in the brand-name drug.
- The generic drug has the same strength, conditions of use, dosage form (such as a tablet or an injectable), and route of administration (such as oral or topical) as the brand-name drug.
- The generic drug performs in the same manner as the brand-name drug.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

The ANDA submitted by drug companies must show the generic drug to be the same as the brand-name drug in these additional ways:

- The inactive ingredients of the generic medicine are acceptable.
- The generic drug meets the same strict manufacturing standards as the brand-name drug.
- The container in which the medicine will be shipped and sold is appropriate, and the labeling is the same as the brand-name drug's labeling (with certain permissible exceptions).

To learn more about how FDA reviews generic medicines, visit What Is the Approval Process for Generic Drugs?

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

An ANDA submitted to FDA for approval must show that:

- **The generic drug is "pharmaceutically equivalent" to the brand** – the generic drug needs to demonstrate that it is the same. The generic must be in the same dosage form and provide the same rate and extent of drug exposure, regardless of the technology used.
- **The manufacturer is capable of making the drug correctly** – Often different companies are involved (such as one company manufacturing the active ingredient and another company manufacturing the finished drug). Generic drug manufacturers must produce batches of the drugs they want to market and provide information about the manufacturing of those batches for FDA to review.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

An ANDA submitted to FDA for approval must also show that:

- **The manufacturer is capable of making the drug consistently** - Generic drug manufacturers must explain how they intend to manufacture the drug, and provide evidence that each step of the manufacturing process will produce the same result each time. FDA scientists review those procedures and FDA inspectors go to the generic drug manufacturer's facility to verify that the manufacturer is capable of making the drug consistently and to check that the information the manufacturer has submitted to FDA is accurate.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

In addition to making the drug consistently, an ANDA submitted to FDA for approval shows that:

- **The "active ingredient" is the same as that of the brand** - An active ingredient in a medicine is the component that makes it pharmaceutically active - effective against the illness or condition it is treating. Generic drug companies must provide evidence that shows that their active ingredient is the same as that of the brand-name drug they copy, and FDA must review that evidence.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

An ANDA submitted to FDA for approval must also show that:

- **The right amount of the active ingredient gets to the place in the body where it has effect** - Two drug products with the same amount of active ingredient may be processed differently for different people. Generic drug companies must perform studies that show that the same amount of drug gets to the bloodstream and that it gets there at about the same time. FDA scientists analyze the results to be sure the generic will produce the same result as the brand-name drug.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

ANDA submitted to FDA for approval must also show that:

- **The "inactive" ingredients of the drug are safe** - Some differences, which must be shown to have no effect on how the drug functions, are allowed between the generic drug and the brand-name drug. Generic drug companies must submit evidence that all the ingredients used in their products are safe, and FDA must review that evidence.
- **The drug does not break down over time** - Most drugs break down, or deteriorate, over time. Brand-name and generic drug companies must do months-long "stability tests" to show that their versions last for a reasonable time. FDA reviews the results of these studies.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

An ANDA submitted to FDA for approval must also show that:

- **The container in which the drug will be shipped and sold is appropriate** - The quality of the drug can deteriorate if its container is not appropriate. Information must be submitted about the containers and FDA must evaluate the information.

- **The labeling is the same as the brand-name drug's labeling** - The drug information label for the generic drugs must be the same as the brand-name drug, with certain permissible exceptions. Sometimes, disputes arise related to the patents or exclusivities a brand-name drug has and the use(s) for which a generic drug can be approved. A generic drug can be approved for a use that is not protected by patents or legal exclusivities, and must remove all references to the legally protected use from the drug's labeling, so long as that removal does not take away information needed for safe use.

Learn more about the approval process for generic drugs on the What Is the Approval Process for Generic Drugs? page.

Approval of Generic Drugs: Abbreviated New Drug Application, Cont.

In addition to the labeling being the same as the brand-name drug's labeling, an ANDA submitted to FDA for approval must show that:

- **Relevant patents or legal exclusivities are expired** - As an incentive to develop new drugs, drug companies may be awarded patents and legal exclusivities that delay the FDA approval of applications for generic drugs. FDA must comply with the delays in review and approval that the patents and exclusivities impose.

Approval of Generic Drugs

A generic drug application must confirm that a generic drug is equivalent to the brand-name drug in the following ways:

- The active ingredient is the same as that of the brand-name drug.
- An active ingredient in a drug is the component that makes it pharmaceutically active — effective against the illness or condition it is treating.
- Generic drug companies must provide evidence that shows that their active ingredient(s) are the same as that of the brand-name drug they copy, and FDA must review that evidence.
- The generic drug is the same strength as the brand-name drug.
- The drug has the same dosage form (such as a tablet or an injectable).

Approval of Generic Drugs, Cont.

A generic drug application must confirm that a generic drug is equivalent to the brand-name drug in the following ways:

- The drug has the same route of administration (such as oral or topical).
- The drug has the same conditions of use.
- The drug provides the same rate and extent of drug exposure.
- The inactive ingredients of the medicine are acceptable.
- Some differences in inactive ingredients, which must be shown to have no effect on how the drug functions, are allowed between the generic and the brand-name version.
- Generic drug companies must submit evidence that all the ingredients used in their products are acceptable, and FDA must review that evidence.

Approval of Generic Drugs, Cont.

Additionally, a generic drug application must confirm that a generic drug is equivalent to the brand-name drug in the following ways:

- It lasts for the same amount of time.
- It meets the same strict manufacturing standards as the brand-name drug.
- The container in which the drug will be shipped and sold is appropriate.
- The labeling is the same as the brand-name drug's labeling (with certain permissible exceptions).
- Relevant patents or exclusivities are addressed.

The ANDA process does not, however, require the drug applicant to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. This allows the generic drug to be brought to market more quickly and at lower cost, allowing for increased access to medications by the public.

Read more about the standards generic drugs must meet to receive FDA approval.

Read more facts about generic drugs.

Generic Drug Misconceptions

However, some Americans are still wary of generics due to misconceptions.

Generic and brand-name medicines have the same:

- Active ingredient(s)
- Conditions of use
- Route of administration
- Dosage form
- Strength
- Labeling (with certain permissible differences)

But generic medicines can look different from brand-name medicines. Allowable differences in size, shape, and color do not impact how medications work.

And generic medicines can cost less money. Generic medicines tend to cost less than their brand-name counterparts because they do not have to repeat animal and clinical (human) studies that were required of the brand-name medicines to demonstrate safety and effectiveness. Learn more about generic drugs.

Read more about the importance of the physical characteristics of generic drugs in an article entitled, *From our perspective: The importance of the physical characteristics of generic drugs*.

Knowledge Check

Question 1

Identify the two regulatory pathways for nonprescription OTC drugs:

a) NDA and OTC monograph

b) NDA and active ingredient list

c) Inspection Certificates from the manufacturer and OTC Monograph

d) OTC monograph and patent approval

Correct answer feedback: Correct! The correct answer is a. New Drug Application and OTC Monograph are the two regulatory pathways for nonprescription or OTC drugs.

The Hatch-Waxman Amendments

Multiple manufacturers are often approved to market a single generic medicine, creating competition in the market place and often resulting in lower prices. However, why does it seem to take a long time for a generic version of a brand name product to reach the pharmacy?

In addition to establishing the approval pathway for generic drug products, Hatch-Waxman Amendments also include provisions that involve patents and exclusivities.

Patents/Exclusivity

Patents and exclusivities are two different forms of protection for qualifying drug products that may affect how and when certain generic versions of those drug products are approved. A drug patent is a property right granted by the United States Patent and Trademark Office (USPTO) anytime during the development of a drug. Patents protect a drug manufacturer's invention (for example, a new drug or a new use for a drug) and prevent other manufacturers from marketing products covered by the patent.

Generally, a patent term is 20 years from the date of filing with the USPTO. FDA does not enforce patents or evaluate patent validity or infringement.

Read this CDER Conversation about patents and exclusivities for generic drug products.

Patents/Exclusivity, Cont.

An exclusivity provides limited protection from new competition in the marketplace and precludes submission, in some cases, or approval of certain ANDAs for prescribed periods of time. Certain exclusivities for qualifying brand name drugs and generic drugs were established in the Hatch Waxman Amendments as part of the Drug Price Competition and Patent Term Restoration Act of 1984. A type of exclusivity for brand-name "orphan" drug products was established by the Orphan Drug Act of 1983. Moreover, exclusivity extensions are available for certain pediatric-related uses of drug products, and for qualifying antibiotic drug products. The FDA administers all of these exclusivities.

Exclusivities for brand-name drug products are intended to provide incentive for brand-name companies to develop new drug products and to find new uses for already approved drug products. Exclusivities for certain generic drugs provide incentive for generic drug companies to challenge brand-name companies' patents.

Access the Orange Book, an online publication where FDA lists patent and exclusivity information.

The FDA provides tools to keep you informed, including a download for the Orange Book Express App.

Drug Competition Action Plan

FDA's Drug Competition Action Plan addresses the challenges related to developing generic drugs and promotes more generic competition. It is an important part of the Agency's broader effort to foster

generic competition and help address the high cost of drugs and improve patient access to important medicines.

In addition to taking action to enhance generic competition, the FDA is working to make generic drug development more transparent, efficient, and predictable. The Agency is working to reduce approval times and to enhance the efficiency of certain aspects of the submission process for generic drug applicants.

Knowledge Check

Question 2

Which legislative action establishes the approval pathway for generic drug products?

a) Drug Competition Action Plan

b) Hatch-Waxman Amendments

c) BPCI Act

d) Biosimilars Action Plan

Correct answer feedback: Correct! The correct answer is b. The Hatch-Waxman Amendments establish the approval pathway for generic drug products.

Biosimilars

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This pathway was established as a way to enable approval of more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition.

FDA requires that biosimilar and interchangeable biological products meet the Agency's rigorous approval standards. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.

Visit the Biosimilars Web site to learn more about biosimilars.

Biosimilars, Cont.

What is a biological product?

"Biological product" is defined in the Public Health Service Act. Biological products are regulated by FDA and are used to prevent, treat, and cure diseases and medical conditions. Biological products are generally large, complex molecules. These products may replicate natural substances such as enzymes, antibodies, or hormones in the body and may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs.

What is a biosimilar product?

A biosimilar is a biological product that is highly similar to an FDA-licensed reference product and has no clinically meaningful differences from the FDA-licensed reference product in terms of safety, purity, and potency.

What is an interchangeable product?

An interchangeable product is a biosimilar product that may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. To be licensed as interchangeable with the FDA-licensed reference product, an application must include information demonstrating that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the application must contain information sufficient to demonstrate that there is not a greater risk from alternating or switching between use of the product and its reference product in terms of safety or reduced efficacy.

What is the difference between a biosimilar and an interchangeable product?

An interchangeable product, in addition to being biosimilar, meets additional requirements based on further evaluation and additional data and information, as appropriate. A product approved as an interchangeable product may be substituted for the reference product without consulting the prescriber, depending on state law.

Many states have laws that address pharmacy-level substitution, and the specific laws vary from state to state. For information about prescription and substitution laws, check with your State Board of Pharmacy.

Biosimilars: Are Biosimilars the Same as Generic Drugs?

Biosimilars and generic drugs are both FDA-approved medications that may offer more affordable treatment options to patients; however, there are differences between biosimilars and generic drugs. Biosimilars and generics are approved through different abbreviated pathways that avoid duplicating certain costly clinical trials. A generic drug is a "duplicate" of a previously approved drug that is approved by FDA in an abbreviated new drug application submitted under the Federal Food, Drug, and Cosmetic Act. A biosimilar is a biological product that is highly similar to an FDA-licensed reference product and has no clinically meaningful differences from the FDA-licensed reference product in terms of safety, purity, and potency, and is approved by FDA in a biologics license application submitted under the Public Health Service Act. Both biosimilar and generics go through a rigorous review process. Once FDA-approved, these medications are just as safe and effective as the reference products to which they are compared.

In contrast to a chemical drug, which is synthesized and can be generally copied, a biological product generally is made from natural and living sources and cannot be exactly copied. So, the information needed to demonstrate that a biological product is biosimilar to another biological product can be much more extensive than what is needed for a generic drug.

Biosimilars, Cont.

The availability of biosimilar and interchangeable biological products that meet FDA's robust approval standards can increase patient access to lifesaving or life-altering medications and potentially lower

costs through competition. The Biosimilar User Fee Act and subsequent amendments (BsUFA) is the agreement that helps fund the review and approval of biosimilar and interchangeable products.

The Promise of Biosimilars [VIDEO TRANSCRIPT]

DR. SCOTT GOTTLIEB: The first biosimilar was approved in 2015. Since then there's been additional biosimilar products approved by the FDA, but there's a very rich pipeline. More and more of the drugs we see coming on to the market are biological products, and so a lot of the important treatments for cancer, a lot of the important treatments for rare diseases, for different disorders, are biological products.

NARRATOR: More treatment options… more access to medications that can save lives … and the possibility that market competition will drive down the costs of health care. These are the promises that biosimilars offer.

DR. LEAH CHRISTL: The first thing to understand about biosimilars is that they are biological products. A biological product is a very complex product. It's produced in a living system, such as bacteria, a yeast, or a cell.

NARRATOR: Biological products have transformed the treatment of many serious illnesses, including some cancers, digestive diseases, dermatological conditions, and rheumatoid arthritis. Biological products are innovative, and that innovation can come with a high cost. That's where biosimilars come in.

DR. SCOTT GOTTLIEB: Much like we have generic drugs that are copies of small molecule drugs, we now have a pathway to allow for the approval of biosimilar products, which are similar to, and sometimes interchangeable with, an FDA-approved biological product.

DR. LEAH CHRISTL: For biological products, we didn't have an abbreviated approval pathway, so the only way to come to market was to have that full data package, which can be very expensive to develop those products. And you see that reflected in the cost of the products in the marketplace.

NARRATOR: FDA's abbreviated pathway can reduce development costs and time to market, which can open the door to the release of more biosimiliars...and in turn potentially lower costs for patients. This pathway begins with analytical studies.

DR. LEAH CHRISTL: A biosimilar product needs to show that it's highly similar to the product it's comparing itself to, with a reference product, and also that there are no clinically meaningful differences between the products.

DR. SCOTT GOTTLIEB: The health care community can certainly have full confidence in an FDA-approved biosimilar. It will be established in the product's labeling how the product should be used, and so in certain situations these products won't be interchangeable with the already approved products and in some cases they will be, but that's going to be clearly defined in the labeling, and practitioners will be able to get access to that information very easily.

NARRATOR: For both practitioners and their patients, biosimilars are changing the landscape of health care...using innovation to save lives. FDA-approved biosimilars are safe and effective and may be delivered at a lower cost. The promise of biosimilars is becoming a reality.

DR. SCOTT GOTTLIEB: They're just as safe and effective as their traditional counterparts, and they could provide enormous savings to consumers through more product competition.

NARRATOR: To learn more, please visit http://www.fda.gov/biosimilars.

Biosimilars, Cont.

FDA released the Biosimilars Action Plan (BAP) to provide information about the key actions the agency is taking to encourage innovation and competition among biological products and the development of biosimilars. The BAP builds on the Agency's progress in implementing the approval pathway for biosimilar and interchangeable products.

You may find additional information on biosimilars on our CDERLearn course offerings page.

The searchable "Purple Book Database of Licensed Biological Products" contains information about all FDA-licensed biological products regulated by CDER, including licensed biosimilar and interchangeable products, and their reference products, and FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by CBER.

Regulatory Changes for Certain Biological Products

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that on March 23, 2020, the small subset of "biological products" approved under the Federal Food, Drug, and Cosmetic Act, such as insulin and human growth hormone, transition to being regulated as biological products under the Public Health Service Act. This transition was a regulatory action in which an approved marketing application for a transition biological product was deemed to be an approved biologics license application. This transition makes it possible for manufacturers to submit and the FDA to approve marketing applications for biosimilar and interchangeable products that reference a transition biological product, which will help ensure that the market is competitive, and patients may have more affordable access to the medications they need.

More information can be found on the "Deemed to be a License" Provision of the BPCI Act page.

Office of Pharmaceutical Quality

Just as OPQ is involved in assuring new drug quality, it is equally tasked with the responsibility of creating a uniform drug quality program across all human drug product areas including OTCs, generics, and biosimilars. OPQ also encourages the adoption of emerging technologies to enhance pharmaceutical quality and potentially reinvigorate the pharmaceutical manufacturing sector.

Lesson 2 Summary

Some key points to remember include:

- Nonprescription drugs may be marketed under an approved NDA (or ANDA) or under an OTC drug monograph.
- FDA ensures that generic products perform the same as their respective brand-name reference products.
- Generic drug applicants must submit an ANDA demonstrating that the generic medicine is the "same" as (including bioequivalent to) the brand-name version.

- The Drug Competition Action Plan addresses the challenges related to developing generics and promotes more generic competition to brand-name medicines, helping to address the high cost of drugs and improve patient access to important medicines.
- A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an FDA-approved reference product.
- The Biosimilars Action Plan provides information about the key actions the Agency is taking to encourage innovation and competition among biological products and the development of biosimilars.

Congratulations! You have successfully completed this lesson!

Module 2: Drug Safety, Communication, and Promotion

Lesson 1: Safety of Regulated Medical Products

Introduction

The safety of regulated medical products is a priority and a core business activity of the Agency. Since it was established more than a century ago, FDA has served as the nation's first consumer protection agency. Some patients may incorrectly believe that the "FDA seal of approval" means no risk.

Introduction, Cont.

The fact is that all drugs have both benefits and risks, and the evaluation of a drug's risk-benefit balance forms the basis of FDA's regulatory decision for the pre-and post-approval assessment process. To be approved for marketing, a drug must be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.

Introduction, Cont.

FDA's risk-benefit analysis takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a New Drug Application (NDA) or a Biologics License Application (BLA) along with other sources of data, and includes consideration of the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.

Everyone (FDA, health care professionals, and consumers) has a stake in understanding and evaluating the benefit/risk ratio associated with drugs. The FDA works with manufacturers to communicate the safety information.

Introduction, Cont.

As important as the FDA activities are to bring new and innovative treatments to the market, the safety of regulated medical products is also a priority and a core business activity of the agency. Since it was established more than a century ago, the FDA has served as the nation's first consumer protection agency. Patients may believe that the FDA seal of approval means no risk. The fact is that drugs have benefits and risks. Everyone -- FDA, health care providers and consumers -- has a stake in understanding and evaluating the benefit/risk ratio associated with drugs. The FDA works with manufacturers to effectively communicate this benefit/risk ratio.

Learning Objectives

To understand drug safety, communication, and promotion, we will take a look at how FDA oversees the safety of regulated medical products and how FDA analyzes the science behind safety.

After completing this lesson, you should be able to:

- Identify FDA's post-approval drug safety programs and initiatives.
- List the various drug risk communication tools used to detect and disseminate information about drug risks to the public.
- List the various regulatory actions that FDA may take as a result of new safety findings.

FDA Pre- and Post-approval Process

Although FDA has one of the most rigorous pre-approval processes in the world, even well-conducted, randomized, controlled clinical trials cannot uncover every potential safety issue, nor are they expected to do so.

Once a drug is approved and marketed, we often gain additional information as the drug is used and studied in broader and more diverse populations. We will discuss different techniques that FDA employs to monitor post-approval use.

MedWatch Reporting Program

Beyond the clinical study of drugs, the Agency must also consider how people will actually use newly approved drugs once they are marketed.

The clinical trial experience may not perfectly reflect how the drug will be used in the health care system; therefore, the true outcomes for patients may be unknown when they take an approved drug product.

This is where adverse drug experience reporting from sponsors, health care professionals, and consumers is a vital link in ensuring that drugs on the market remain safe and effective.

MedWatch Reporting Program, Cont.

The most widely known reporting system for adverse events or product problems for marketed drugs, biologics, devices, and other FDA-regulated products is the MedWatch program. For CDER products, four types of adverse events may be reported:

- Adverse drug reactions
- Product quality problems
- Medication errors
- Therapeutic failure/inequivalence

Visit the MedWatch Web page for more information.

MedWatch Reporting Program, Cont.

MedWatch is designed to enhance the effectiveness of the post-approval surveillance of medical products as they are used in clinical practice. The adverse event reporting system allows FDA safety reviewers to rapidly identify potentially significant health hazards associated with medical products.

The FDA MedWatch Reporting Program offers everyone an opportunity to report adverse events and problems with medical products to FDA. Because FDA cannot require the public to report adverse events, adverse event reports from members of the public are considered voluntary. Conversely, adverse event reporting is mandatory for manufacturers in the drug and devices industry.

In the post-market setting, safety information has to flow two ways. We rely on manufacturers, health care professionals, and consumers to report adverse event experiences to the Agency. In turn, we communicate what action FDA has taken to increase the safety of medical products.

Access the MedWatch Voluntary Report Form for Health Professionals or Consumers/Patients.

Knowledge Check

Question 1

Which is the most widely known reporting system for adverse events or product problems for marketed drugs, biologics, devices, and other FDA-regulated products?

a) FAERS

b) MedWatch reporting

c) Consumer reports

d) National EMS Information System

Correct answer feedback: Correct! The correct answer is b. MedWatch reporting is the most widely known reporting system for adverse events or product problems for marketed drugs, biologics, devices, and other FDA-regulated products.

Drug Safety Communications (DSCs)

FDA uses DSCs to alert health care professionals, patients, and consumers about newly observed safety information on FDA-approved drugs and to offer advice as to how these drugs may best be used in light of this new information. DSCs are posted on FDA's Web page and also disseminated through email updates, Twitter, and podcasts.

Visit the DSC site to learn more.

Listen to the DSC podcasts.

Drug Safety Oversight Board and Drug Risk Monitoring Board

The Drug Safety Oversight Board (DSB) advises the Center Director on the management of and communication on significant and often emerging drug safety issues. The DSB provides a forum for discussion and input regarding drug safety issues. Created in 2005, the DSB is composed of representatives from FDA and eight other federal government agencies.

The primary objectives of the Board are to:

- Provide independent oversight and advice to CDER leadership on the management of significant drug safety issues, and
- Coordinate and manage the flow of emerging safety information to health care professionals and patients.

Drug Safety Oversight Board and Drug Risk Monitoring Board, Cont.

The Drug Risk Monitoring Board (DRMB) will coordinate high-risk, cross-cutting safety activities by:

- Facilitating decision-making across the center as it concerns major safety issues with marketed products,
- Developing clear and consistent guidance to provide for an appropriate response to and communication about major safety issues, and
- Communicating recommendations, decisions, and actions to the Center Director and throughout the center as appropriate.

The DRMB will continue the steering committee's work to facilitate and coordinate all new and existing marketed product safety initiatives across CDER.

Drug Safety Regulatory Actions

Discovery of a safety signal may result in a range of FDA regulatory actions. FDAAA authorizes FDA to require and order labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug. FDAAA also gives FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) and the authority to require applicants to conduct post-market safety studies or clinical trials. The goal of each regulatory action is the same: to protect public health.

Drug Safety Regulatory Actions, Cont.

Required Safety Labeling Changes

The drug labeling contains a summary of the essential information needed to use the product safely and effectively. The labeling is available from your local pharmacist, on drug manufacturers' Web sites, in FDA's Drugs@FDA database, on DailyMed, on FDALabel, as well as other Web sites. Labeling must be changed if new information becomes available that causes the labeling to become inaccurate, false, or misleading. FDA can also require drug manufacturers to change the drug labeling to add new safety information if it becomes available. Visit Drug Labeling Safety to find information on recent changes to drug labeling.

Medication Guides

Medication Guides are FDA-approved patient labeling that accompany certain prescription drugs that pose a serious and significant health concern. Medication Guides, which accompany each new prescription and refill by the pharmacist:

- Address issues that are specific to particular drugs and drug classes.
- Contain FDA-approved information written in consumer-friendly language to help patients make decisions about the use of their medications and allow them to be informed on how to avoid serious adverse drug events.

Learn more about Medication Guides.

Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh

its risks. REMS are generally designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a small proportion of medications require a REMS. The REMS document, which is enforceable, is included with the REMS approval letter for a product and describes the elements that an applicant is required to implement. A REMS may include one or more of the following elements:

- A Medication Guide, a patient package insert, and/or communication plan
- Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
- Health care providers who prescribe the drug must have particular training or experience
- Pharmacists or others who dispense drugs must be specially certified
- Drug may be dispensed only in certain health care settings (e.g., infusion settings, hospitals)
- Drug may be dispensed with evidence of safe-use conditions such as laboratory test results
- Each patient using the drug must be monitored
- Each patient using the drug must be enrolled in a registry, or a requirement that the drug must be dispensed with documentation of certain safe use conditions

Note that a product may have a Medication Guide as part of labeling or as an element of a REMS.

Currently approved REMS are available on REMS@FDA.

Post-marketing Requirements

Post-marketing Requirements (PMRs) include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations. FDA can require a sponsor to conduct a safety PMR to assess a known serious risk related to use of the drug, assess signals of serious risk related to use of the drug, or identify an unexpected serious risk when available data indicate the potential for a serious risk.

Indication Withdrawal

By law, drugs must be demonstrated to be safe and effective for their intended use in order to merit FDA approval. The Federal Food, Drug & Cosmetic (FD&C) Act states that if a drug approved under an accelerated approval pathway fails to verify clinical benefit in confirmatory studies, or if other evidence demonstrates that the product is not safe or effective under its conditions for use, FDA may withdraw approval.

Drug Safety Regulatory Actions, Cont.

Drug Safety-related Labeling Changes

Since the class of ethinyl estradiol-containing combination hormonal contraceptive products was approved, FDA became aware of reports of liver enzyme elevations in clinical trial subjects using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products (containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir).

FDA notified sponsors of ethinyl estradiol-containing contraceptive products of the requirement to update product labeling with information about the serious risk of liver enzyme elevations with concomitant Hepatitis C treatment.

Indication Withdrawal

FDA approved a drug product with a metastatic breast cancer indication through the Agency's accelerated approval pathway, meaning that the drug was approved based on promising results from one study that suggested that the drug could delay tumor growth and patient death.

The drug company began marketing the drug, but in accordance with accelerated approval, continued two additional (post-marketing) clinical trials. The post-marketing results showed only a small effect on tumor growth and no evidence that the drug caused patients to live any longer or have a better quality of life. FDA ultimately concluded that the benefits of the drug did not outweigh its risks and the Agency withdrew approval of the indication.

Knowledge Check

Question 2

Where can you find information about drug risks to the public disseminated by FDA?

a) Local news channel

b) Commercial advertisements

c) Drug Safety Communications (DSCs) on the FDA Web site

d) Informational pamphlets at a health care provider's office

Correct answer feedback: Correct! The correct answer is c. You can find information about drug risks to the public disseminated by FDA on the Drug Safety Communications page on the FDA Web site.

Knowledge Check

Question 3

Identify the regulatory action FDA may take as a result of new safety findings:

a) Publish safety labeling changes

b) Attend congressional hearings

c) Issue an amendment to the relevant code or policy

d) Ban pharmacies from carrying the impacted drug or biologic

Correct answer feedback: Correct! The correct answer is a. Publishing safety labeling changes is the regulatory action FDA may take as a result of new safety changes.

Lesson 1 Summary

Some key points to remember include:

- Drug safety is of vital importance to the health of the American public and to the mission of FDA.
- It is essential that information be obtained during the entire drug lifecycle.
- CDER uses a variety of electronic communication channels to provide timely safety information to both the health care community and patients.
- Discovery of a product-related risk may result in an array of FDA regulatory actions.

Lesson 1 Summary, Cont.

Some key points to remember include:

- FDA employs several drug risk communication tools to disseminate information about drug risks to the public.
- MedWatch serves as a monitoring system for reporting adverse events for marketed drug products, biologics, and devices.
- Post-marketing requirements or commitments may be issued after a drug product is approved.
- A Risk Evaluation and Mitigation Strategy, or REMS, is a strategy to manage a known or potential serious risk associated with a drug or biological product.

Congratulations! You have successfully completed this lesson!

Lesson 2: Science of Safety

Introduction and Learning Objectives

The emergence of a science of safety is an important new development in FDA.

The science of safety combines the growing understanding of disease and its origins at the molecular level (including understanding of adverse events resulting from treatment) with new methods of signal detection, data mining, and hypothesis-testing studies. The science of safety enables researchers to generate hypotheses and to evaluate drug-related risks and medication errors, including causal factors, in patient populations using drug products.

After you complete this lesson, you should be able to:

- Describe how new science of safety measures and methods are changing the landscape of drug safety.
- Identify post-approval drug safety surveillance initiatives, including the FDA Adverse Event Reporting System (FAERS) and those resulting from FDAAA such as Sentinel.
- Outline the required contents of drug labeling and describe FDA's work on drug product promotion review.
- Describe the tools used in post-approval drug safety surveillance.

Science of Safety Opportunities

Evaluation of safety is performed during the entire drug product lifecycle. If a safety evaluation leads to a conclusion that regulatory action is appropriate, then FDA must consider a number of factors to determine which action is appropriate. If these evaluations lead to regulatory action, multiple factors are considered, including impact on access to the product.

As we discussed in the previous lesson, a clear example is when FDA, after analysis of adverse events, considers whether or not to withdraw a drug from the market for safety reasons. Although withdrawal would eliminate the possibility of further adverse events, it would simultaneously deprive treatment access to patients for whom the drug is effective.

Science of Safety Opportunities, Cont.

If, using methods developed for drug safety evaluation, reviewers can determine that an adverse event is restricted to a small, identifiable segment of the population, the drug or biologic can remain on the market and continue to benefit those who are not at risk for the adverse event.

Post-approval Drug Safety Surveillance Teams

The teams responsible for post-approval drug safety surveillance are assigned based on therapeutic drug class and are located within the Office of Surveillance and Epidemiology. For example, there are teams that evaluate post-approval data for cardiovascular products, anti-viral medications, and gastrointestinal drugs. These teams work with clinical teams in the Office of New Drugs to review and evaluate the safety of drug products.

Safety Evaluators

Within these teams, the role of safety evaluators is to detect and assess safety signals for marketed drug products. They work closely with medical scientific reviewers who review new drugs, so that potential safety signals are assessed in the context of existing preclinical, clinical, or pharmacologic knowledge of the drugs in question.

Epidemiologists

CDER epidemiologists evaluate product-related risks through various methods and tools including conducting studies in computerized databases, reviewing protocol and studies conducted in various data and the published literature.

The conclusions from these teams may be incorporated into risk management strategies, such as patient registry or pharmacy certification requirements. The findings from safety evaluations may be the basis for establishing a new, or modifying an existing REMS, requiring safety labeling changes, and/or requiring a company to conduct a post-market safety study or trial.

Knowledge Check

Question 1

What is the role of safety evaluators?

a) To ensure consumers know how to take the drug product safely

b) To detect and assess safety signals for marketed drug products

c) To educate healthcare providers and pharmacists on the proper methods to disseminate the drug product

d) To evaluate product-related risks through various methods and tools

Correct answer feedback: Correct! The correct answer is b. Safety evaluators detect and assess safety signals for marketed drug products.

FAERS (FDA Adverse Event Reporting System)

The FDA Adverse Event Reporting System (FAERS) – formerly AERS – is a database that contains information on adverse events medication error reports, and product quality complaints submitted to FDA.

FAERS (FDA Adverse Event Reporting System), Cont.

The database is an important tool in FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. About 95 percent of the 1.4 million MedWatch reports received annually come from drug product sponsors or manufacturers; the remainder come directly from the public. If a manufacturer receives an adverse event report, it is required to send the report to FDA. Reports received are uploaded into FAERS.

Visit the FAERS Web page to learn more about FAERS.

FAERS Strengths

What Are the Strengths of the FAERS System?

Using FAERS, FDA is able to identify new safety concerns that might be related to a marketed product. If a potential safety concern is identified in FAERS, further evaluation is performed.

FAERS Limitations

What Are the Limitations of the FAERS System?

When you view side effects or adverse drug reactions for a drug product in FAERS, it is important to consider the following points:

- **Data Quality:** There are many instances when the same report is submitted by the consumer and the sponsor, and some reports do not contain all the necessary information. The information in FAERS evolves daily and the number of individual cases may increase or decrease over time.
- **Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.
- **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor is it an admission from the reporter that the drug caused or contributed the event.

FAERS Limitations, Cont.

What Are the Limitations of the FAERS System?

When you view side effects or adverse drug reactions for a drug product in FAERS, it is important to consider the following points:

- **Rates of occurrence cannot be established with reports:** The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. The FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.
- **Patients should talk to their doctor** before stopping or changing how they take their medications.
- **Patient Outcomes received in FAERS:** These data describe the outcome of the patient. Serious means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes.

Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug.

However, independent of these limitations, FAERS is sensitive for rare, serious events. If a strong safety signal is detected through all the "noise," it is an indication that a serious safety problem may be occurring with a drug.

Sentinel Initiative

Another tool in FDA's drug safety surveillance program was established through the creation of an "active" post-market safety surveillance system, Sentinel.

The Sentinel Initiative was launched in 2008 in response to the FDA Amendments Act (FDAAA) of 2007. FDAAA mandated that FDA:

- Develop a post-market risk identification and analysis system for medical products.
- Incorporate data on at least 100 million patients by July 2012 from both public and private sources of health care data.
- Have the capacity to both identify and evaluate safety concerns for medical products.
- Operate the system using a framework that protects the privacy and confidentiality of individual health information.

Sentinel Initiative, Cont.

Today, the Sentinel System uses a suite of routine querying tools along with electronic health care data to monitor the safety of regulated medical products. Sentinel is used to proactively assess the safety of drugs, under real-world conditions, that more closely reflect patient care in the United States. This capability enhances drug safety monitoring and enables the FDA to systematically assess safety signals identified during pre-market testing, as well as signals that emerge after drugs are released to the market. Sentinel queries data from a distributed network of Data Partners, so that data security is maintained and patient privacy is protected.

FDA created automated surveillance tools in the Active Risk Identification & Analysis (ARIA) System, which is part of Sentinel. ARIA is available on the Sentinel Initiative Web site. Before FDA can require an applicant to conduct further safety studies on a drug product, FDAAA also requires the FDA to assess

whether this active risk identification and analysis system is sufficient to assess a safety concern prior to requiring a sponsor conduct a post-marketing study on their drug product.

Visit the Sentinel Web page to learn more about the Sentinel Initiative.

Sentinel Data Sources

Sentinel relies on data that are generated from patient interactions with the U.S. health care system through health insurers and health care providers. The principal source of data currently used in Sentinel is health care administrative claims data. These data are maintained in a multi-site distributed data network and undergo extensive quality checks.

Additional types of health care information that complement the claims data in Sentinel are listed below:

- Electronic health records (EHRs)
- Patient-reported outcome information
- Immunization registries
- Disease registries
- Birth and death registries

Sentinel is continuously working to broaden the types of data available for use in accomplishing FDA's goal of advancing an active surveillance system to monitor the safety of FDA-regulated medical products.

Tools in the Sentinel System

Sentinel's routine querying tools include modular programs and software toolkits, which are each used in varying ways to investigate outcomes and/or medical products of interest. Modular programs are categorized based on the type and complexity of the analysis:

- **Signal Identification** queries detect new and unsuspected potential safety concerns.
- **Level 1** modular program queries are descriptive analyses (e.g., utilization of individual drugs or switching between drugs, drug utilization in pregnancy, incidence, or background rates for health outcomes).
- **Level 2** modular program queries are inferential analyses (propensity score analysis, multiple factor matching, self-controlled risk interval design).
- **Level 3** modular program queries are more complex prospective sequential analyses (e.g., self-controlled risk interval design).

There are a variety of automated tools for active safety surveillance. Sentinel tools are publicly available on the Sentinel Web site.

Three Sentinel Centers

In 2019, three distinct Sentinel centers were created. These centers will enhance participation with a wider array of scientific expertise, translate new technologies from emerging fields such as data science and informatics, create laboratories to develop new approaches to using electronic health records, and cultivate a robust scientific community to advance the broader Agency goal of creating a national resource that can support the learning health care system.

1. The Sentinel Operations Center (SOC) will continue to leverage organizational partnerships in the areas of epidemiology, clinical medicine, pharmacy, statistics, health informatics, data science, and network operations to support post-market safety analyses. Through FDA Catalyst, the SOC will also continue to support interventions and interactions with patients and with health care providers.
2. The Innovation Center will develop innovative methods to further advance Sentinel, including exploring novel ways to extract and structure information from electronic health records, such as through use of artificial intelligence (natural language processing and machine learning).
3. The Community Building and Outreach Center will focus on communication and collaboration as well as deepening stakeholder involvement and broadening awareness, access, and use of Sentinel tools and data infrastructure.

Many of the aims of the three Centers are captured in FDA's five-year strategy and road map for Sentinel (2019-2023). The strategy directs Sentinel to reach beyond its current boundaries, to many of the areas described above, while preserving capabilities and key accomplishments.

Knowledge Check

Question 2

What is the function of the Sentinel Initiative?

a) To monitor the number of active prescriptions for a certain marketed drug

b) To proactively assess the safety of drugs under real-world conditions that more closely reflect patient care in the United States

c) To monitor the number of class action lawsuits against a manufacturer of a marketed drug

d) To monitor the risk of a biological pandemic

Correct answer feedback: Correct! The correct answer is b. The Sentinel Initiative proactively assesses the safety of drugs under real-world conditions that more closely reflect patient care in the U.S.

Future of Drug Safety

As a result of the Agency's core business activities focusing on improving safe use, good risk assessment, risk management, and pharmacovigilance practices, FDA's strategy for modernizing the drug safety system continues to advance.

Future of Drug Safety, Cont.

So, what is the future of drug safety? The future of drug safety will focus on biomarkers, diagnostics, human factors, increased medical safety education for patients and practitioners, and more.

Research into approaches to personalized medicine will allow FDA to predict through genomics who is and who is not likely to experience a drug's side effects. It will also allow FDA to better predict who will respond to and benefit from a drug, and who will not.

Knowledge Check

Question 3

Approximately 95% of the 1.4 million MedWatch reports received annually come from:

a) Drug product sponsors or manufacturers

b) The public

c) Healthcare providers

d) Pharmacies

Correct answer feedback: Correct! The correct answer is a. Approximately 95% of the 1.4 million MedWatch reports received annually come from drug product sponsors or manufacturers.

Knowledge Check

Question 4

FDA-approved patient labeling includes:

a) Instructions for use, Medication Guides, and patient package inserts

b) Instructions for use, manufacturer's coupon, and side effects

c) Medication Guides and dietary indications

d) Patient package inserts only

Correct answer feedback: Correct! The correct answer is a. FDA-approved patient labeling includes Instructions for Use, Medication Guides, and patient package inserts.

Lesson 2 Summary

Some key points to remember:

- The FDA Adverse Event Reporting System, known as FAERS, is the database into which all drug and biological drug adverse events received by FDA are entered.
- The Sentinel System, proactively monitors medical product safety, provides a critical engine for methodological innovation, and serves as a platform to advance the science of real world evidence. The Sentinel System employs a technique called "data mining," which allows evaluators to extract meaningful, organized information from large complex databases.

Congratulations! You have successfully completed this lesson!

Module 3: Drug Quality and Quality Management

Lesson 1: Drug Quality

Introduction: Drug Quality and Public Health

So far, this presentation has touched on the core activities of new drug development and drug safety.

The third core CDER activity is its mission to promote and protect public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor-quality drugs, while also ensuring product availability.

The Office of Pharmaceutical Quality (OPQ) and the Office of Compliance work together to help ensure the quality of drug products throughout their lifecycle.

Learning Objectives

After completing this lesson, you should be able to:

- Describe the roles of the OPQ and the Office of Compliance.
- Describe the importance of compliance with good manufacturing practice regulations.

OPQ: One Quality Voice

We know that poor drug quality or manufacturing issues such as lack of sterility assurance, impurities, and particles in the drug vial can lead to patient injury, product recalls, plant shutdowns, and drug shortages. OPQ was formed in January 2015 to simplify and streamline FDA processes that monitor drug quality throughout the product lifecycle, including assessment of NDA, ANDA, and BLA submissions, post-market process improvements, and surveillance inspections of related manufacturing facilities worldwide. This enables the Agency to respond quickly to detected problems and proactively address potential areas of quality concerns, prior to product quality problems occurring.

OPQ: One Quality Voice, Cont.

Quality is the basis of everything we do at FDA. Without quality, we cannot be confident that a drug is safe and effective. OPQ works to assure that quality medicines are available for the American public and to prevent unsafe products from reaching consumers.

OPQ's responsibilities and core activities include:

- Integrated review of applications and inspections
- Policy development that establishes and communicates clear standards for quality
- Risk-based evaluation of clinically relevant product attributes which may include attributes that impact delivery and human factors
- Improved surveillance and data management to proactively address quality concerns
- Providing cross-office Product Quality Project Management support
- Holding industry accountable for quality

The Office of Compliance

The Office of Compliance similarly combines strategies and actions to minimize consumer exposure to unsafe, ineffective, and poor-quality drugs. The Office of Compliance is responsible for:

- Managing programs that help to ensure that prescription and OTC drugs are properly marketed and labeled.
- Managing programs that help to protect the security of the drug supply chain and prevent distribution of counterfeit drugs into the United States, and evaluating and conducting (or coordinating) inspections of clinical trial sites.
- Maintaining state-of-the-art laboratories that can test all types of drug products and active ingredients to evaluate their quality.
- Developing and implementing compliance policy and taking advisory actions to protect the public from adulterated drugs.

The Office of Compliance, Cont.

The Office of Compliance plans, develops, and directs compliance strategies and actions that are patient-focused and risk-based to secure the safety, efficacy, and quality of the nation's drug supply. The Office of Compliance is tasked with monitoring the data integrity and product quality for human drugs through results of inspections and product testing, and other pre- and post-market surveillance activities. The Office identifies drug products that violate the Food, Drug, and Cosmetic Act, and it targets compliance actions against products with violations of the law that pose the greatest risk to public health. The Office of Compliance leads our efforts to maximize the use of new and existing statutory authorities in ensuring industry compliance with Federal drug quality standards, minimizing the risks inherent in the drug supply chain, and protecting patients against sub-standard and potentially dangerous drugs. Some new legal authorities include enhanced authority to stop the importation of potentially dangerous drugs and stronger inspection tools.

OPQ and Office of Compliance

OPQ and the Office of Compliance both play an important role when it comes to quality. So what's the difference between these two offices?

OPQ

- Focuses on establishing quality standards and guidance
- Assesses all application types—BLA, NDA, and ANDA—to evaluate quality before marketing approval
- Determines facility inspection procedures (Compliance Programs)
- Decides on inspection frequency using risk-based approaches
- Evaluates quality defect information to determine need for agency intervention
- Tests drug samples to verify quality of marketed drugs, develops novel analytical methods, and evaluates novel technologies

Office of Compliance

- Focuses on enforcement operations and policy related to correcting violations of quality standards
- Supports enforcement by working with industry and taking appropriate actions to ensure that industry complies with Federal laws and regulations
- Pursues related responsibilities in other statutory areas such as misbranding, export certificates, recalls, import surveillance, and more

Post-approval Surveillance

One of OPQ's activities is to manage post-approval surveillance programs to reduce potential consumer exposure to risks of unsafe or ineffective drugs, including risks to product quality that may arise at the manufacturing site.

You may be wondering why, if FDA inspected the manufacturing site before approval, there may be post-approval concerns regarding manufacturing or quality risks. The answer is actually quite complex.

Manufacturing processes and the technology used to manufacture drug or biological drug products are not static processes. Methods, standards, and technology are constantly changing.

The staff in OPQ, in collaboration with the Office of Compliance, help ensure that there is uniform interpretation of these standards and develop policies to achieve high product quality through application of current good manufacturing practice (CGMP) regulations – an essential element to protecting public health.

OPQ also evaluates information about how a drug performs once it's distributed. This information may come from consumer complaints and defect reports or testing by FDA's laboratories.

Knowledge Check

Question 1

OPQ is responsible for:

a) Developing policy that establishes and communicates quality standards governing industry and agency activities.

b) Maintaining reports on adverse effects from drug products.

c) Proofreading Medication Guides and patient package inserts.

d) Designing advertisements for new marketed drugs.

Correct answer feedback: Correct! The correct answer is a. The Office of Pharmaceutical Quality (OPQ) is responsible for developing policy that establishes and communicates quality standards governing industry and agency activities.

Knowledge Check

Question 2

One of the responsibilities of the Office of Compliance is:

a) Conducting research testing on investigational drug products.

b) Designing, developing, and implementing programs to facilitate the incorporation of patient input into decision-making.

c) Leading the areas of technology transfer, data mining, health information technology, science and research oversight, and knowledge management.

d) Managing programs that help to ensure that prescription and OTC drugs are properly marketed and labeled.

Correct answer feedback: Correct! The correct answer is d. One of the responsibilities of the Office of Compliance is managing programs that help to ensure that prescription and OTC drugs are properly marketed and labeled.

Current Good Manufacturing Practice (CGMP) Regulations

Consumers and health care professionals expect that FDA-approved medicines meet quality standards to be safe and effective and provide the labeled benefits.

FDA is committed to helping manufacturers understand and implement modern quality management techniques and risk management approaches to comply with the requirements of the Agency's CGMP regulations.

Quality should be built into the product through thoughtful design of the product formulation and manufacturing process and through an effective control strategy, rather than through reliance on end-product testing alone.

Read more information on CGMPs.

Current Good Manufacturing Practice (CGMP) Regulations, Cont.

What are CGMPs?

CGMP refers to the Current Good Manufacturing Practice regulations and is applicable to all drugs, human as well as drugs for animals. There are CGMP regulations established and enforced by the FDA for certain types of drugs, including finished pharmaceuticals and positron emission tomography drugs. CGMPs provide for systems that assure proper design, maintenance, monitoring, and control of manufacturing processes and facilities.

What is the goal of CGMPs?

The goals of CGMPs are to prevent and correct production mistakes and inefficiencies that pose undue risks to consumers. CDER staff work to improve policies that are making better use of the Agency's resources through more targeted and effective inspections. To advance this mandate, CDER staff are tasked with:

- Ensuring that drugs requiring premarket approval are manufactured in facilities operated in a sufficient state of control to ensure drug safety, identity, strength, quality, and purity
- Establishing a risk-based approach to the selection of manufacturing facilities for routine surveillance inspections
- Taking administrative or enforcement actions to ensure conformance with the anti-adulteration provisions of the Federal Food, Drug, and Cosmetic Act
- Reviewing information regarding foreign and domestic manufacturing facilities in drug applications
- Operating the Drug Recall Program
- Coordinating efforts to assist the Drug Shortages Program

Why are CGMPs important?

Adherence to the CGMP regulations helps assure the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. CGMPs ultimately help to prevent instances of contamination, deviations, failures, and errors. This helps assure that drug products meet their quality standards.

CGMPs set the stage for a culture of commitment to quality; it is important to note that CGMPs are **minimum** requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality management techniques and risk management approaches that exceed these minimum standards. Some pharmaceutical manufacturers are already developing and

implementing novel technological approaches that improve drug quality and ensure availability. For example, use of an emerging technology called "continuous manufacturing," where pharmaceuticals are manufactured in a continuous flow, from starting materials to finished product, using on-line testing and computerized control systems, promises to:

- Reduce throughput time to a few days.
- Allow for equipment utilization rates up to 95 percent.
- Dramatically reduce the risk of production failure.
- Minimize scale-up problems.
- Rapidly adjust production to meet demand.
- Enable rapid detection and correction of adverse trends to maintain quality.

Complying with CGMP Regulations

OPQ develops and manages inspectional programs designed to provide objective and fact-based evaluations of manufacturing and control operations using the CGMP regulations as the standard.

Complying with CGMP Regulations, Cont.

The Office of Regulatory Affairs (ORA), in coordination with CDER staff, inspect pharmaceutical manufacturing facilities worldwide. These staff are trained in science and CGMPs and document observations regarding whether the manufacturer is complying with CGMP regulations. For pre-approval inspections, working collaboratively with the Office of Compliance and ORA, OPQ staff evaluate inspectional findings relating to the conditions and practices in facilities where drugs are manufactured, packed, tested, and stored. The Office of Compliance and ORA coordinate to evaluate inspectional findings from surveillance inspections.

Complying with CGMP Regulations, Cont.

Inspections that discover more significant and potentially serious manufacturing problems and violations are referred to the Office of Compliance for resolution. The Office of Compliance may make appropriate use of any enforcement tools provided for in the statute to exercise correction and mitigate or prevent risk to patients.

When product quality or integrity concerns arise, there are a number of actions that can be taken by FDA or pharmaceutical companies. For example, when warranted, FDA can issue warning letters, seize violative products, or enjoin violative companies. In fact, FDA CGMP inspections find that most manufacturers are sufficiently compliant with the CGMP regulations, and many manufacturers have no significant violations.

Complying with CGMP Regulations, Cont.

CDER also evaluates reports of potentially defective drug products from the public and industry. CDER will often use these reports to help identify sites for inspection or investigation.

Here are some of the activities CDER performs to monitor drug quality and ensure compliance with CGMPs:

- Evaluating reports of drug quality concerns and investigational/inspectional information.
- Issuing and conducting investigational and inspectional assignments.
- Providing guidance on enforcement issues.

- Recommending regulatory actions, collecting and analyzing samples of drugs, both finished products and ingredients, to verify conformance to compendial and labeled standards.

Knowledge Check

Question 3

Identify one of the goals of Current Good Manufacturing Practices:

a) Developing creative marketing and advertisements for FDA

b) Providing effective training for FDA Inspectors

c) Ensuring that drugs requiring premarket approval are manufactured in facilities operated in a sufficient state of control to ensure drug safety, identity, strength, quality, and purity

d) Maintaining databases related to adverse effects reporting

Correct answer feedback: Correct! The correct answer is c. One of the goals of CGMPs is ensuring that drugs requiring premarket approval are manufactured in facilities operated in a sufficient state of control to ensure drug safety, identity, strength, quality, and purity.

Drug Recalls

A drug recall is an example of a voluntary action taken by a company to remove a product from the market. Recalls may be conducted at any time by a company. However, upon initiating a voluntary recall, the company will alert ORA Divisions, which will work with the Office of Compliance, whose staff coordinate the evaluation and classification of drug recalls. The Office of Compliance also works with ORA's field offices in the implementation of recalls and monitors the resolution of related compliance issues.

Search Product Recalls, Market Withdrawals & Safety Alerts on the Recalls, Market Withdrawals, & Safety Alerts page.

Lesson 1 Summary

Some key points to remember, include:

- FDA is committed to helping manufacturers understand and implement modern quality management techniques and risk management approaches to ensure drug quality and availability. The goal of the CGMP regulations is to prevent and correct production problems and inefficiencies and undue risks for consumers.
- OPQ operates programs and policies to verify product quality for human drugs; these include marketing application assessments, facility inspections, drug sampling and testing, and other pre- and post-market surveillance activities.
- The Office of Compliance is involved in evaluating recommendations for enforcement action and implementing actions to correct violations of the law, including CGMP violations.

Congratulations! You have successfully completed this lesson!

Lesson 2: Quality Management and Drug Shortages

Learning Objectives

After completing this lesson, you should be able to:

- Recognize FDA's initiatives to minimize consumer exposure to unsafe, ineffective, and poor quality drugs.
- Identify post-marketing measures to safeguard drug supplies as they move through the drug supply chain.

Post-marketing Safety

While the drug approval process and FDA drug quality programs help to minimize consumer exposure to unsafe, ineffective, and poor-quality drugs, there are also other drug compliance programs that are integral to helping to ensure safety for consumers.

Even after a drug product has completed the development and assessment process and is manufactured in compliance with CGMP requirements, FDA continues to monitor drugs to ensure they do not pose undue risks to the public. To minimize risk, the Office of Compliance is responsible for the following:

Pharmacovigilance Oversight

The Office of Compliance provides oversight of industry pharmacovigilance by selecting and directing inspections of sites to determine compliance with FDA regulations that require drug companies to report post-marketing adverse drug experiences to FDA.

Review of Inspection Reports

The Office of Compliance reviews inspection reports from FDA field staff and evaluates regulatory action recommendations relating to adverse drug experience reporting deficiencies.

REMS Compliance Oversight

The Office of Compliance provides oversight by monitoring for compliance with REMS requirements where a REMS is imposed to ensure the benefits of a drug outweigh its risks.

Knowledge Check

Question 1

How does the Office of Compliance provide oversight of industry pharmacovigilance?

a) By selecting and directing inspections of sites to determine compliance with FDA regulations that require drug companies to report post-marketing adverse drug experience to FDA

b) By monitoring the sales of online pharmacies

c) By sending FDA inspectors to sites to perform secret inspections

d) By monitoring only 503A compounding pharmacies

Correct answer feedback: Correct! The correct answer is a. The Office of Compliance provides oversight of industry pharmacovigilance by selecting and directing inspections of sites to determine compliance

with FDA regulations that require drug companies to report post-marketing adverse drug experience to FDA.

Drugs Marketed Outside of the Approval Process

Although most drug products on the U.S. market have been through the FDA approval process, you may be surprised to learn that this is not true of all drugs currently marketed. Thus, the Office of Compliance also works to:

- Safeguard that prescription and nonprescription drugs are properly marketed and labeled (not misbranded).
- Remove unapproved new drugs from the market and encourage manufacturers to seek FDA approval.
- Protect patients from unsafe, ineffective, and poor-quality compounded drugs, while preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them.

Compounded Drugs

Compounding is often regarded as the process of combining, mixing, or altering ingredients to create medication customized to the needs of an individual patient. Compounded drugs can serve an important role when an FDA-approved drug is not medically appropriate to treat a patient, such as when a patient needs a medication to be made without a certain dye because of an allergy.

However, compounded drugs are not FDA-approved, which means they have not been reviewed by FDA for safety, effectiveness, or quality before they are marketed. If a compounded drug does not meet appropriate quality standards (e.g., if an injectable drug is contaminated, or if a tablet contains too much or too little active ingredient), it can cause serious injury or death.

Compounded Drugs, Cont.

There are two types of compounding pharmacies.

503A

Drugs compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a physician, in accordance with the conditions of section 503A of the FD&C Act are exempt from certain requirements, including CGMP requirements.

503B

Facilities that register with FDA as outsourcing facilities under section 503B of the FD&C Act are primarily overseen by FDA and inspected by FDA according to a risk-based schedule. Drugs compounded in outsourcing facilities in accordance with the conditions of section 503B of the FD&C Act are exempt from certain requirements and are subject to CGMP requirements.

Read a Q&A about compounding.

Unapproved Drugs Program

Unapproved drugs pose a public health risk because they have not been evaluated by the FDA to ensure their safety, effectiveness, quality, and labeling meet standards required by federal law to warrant their

safe use. Many wholesalers, distributors, pharmacy benefit management organizations, hospitals, and other institutions are unaware that some drugs they handle are unapproved.

In 2006, CDER's Office of Compliance launched its Unapproved Drugs Program (previously, the Unapproved Drugs Initiative), a risk-based program that strives to remove from the market those unapproved drugs posing serious risks to patients while preserving access to medically necessary drugs and encouraging manufacturers of unapproved drugs to submit applications to FDA. The Unapproved Drugs Program has resulted in the removal of hundreds of potentially unsafe unapproved prescription drugs from the market using a variety of compliance tools.

Unapproved Drugs Program, Cont.

Some examples include:

- The publication of class-action Federal Register notices alerting the manufacturers of unapproved quinine sulfate, single-ingredient oral colchicine products, and carbinoxamine to remove their products from the market;
- The issuance of Warning Letters for unapproved hydromorphone, morphine sulfate, oral oxycodone, and epinephrine pre-filled syringes; and
- Notifications to firms marketing unapproved versions of FDA-approved cocaine hydrochloride solution and ascorbic acid injectables, requesting that they stop manufacturing and distributing their unapproved products.

In 2011, FDA issued a final guidance, Guidance for FDA Staff and Industry, Marketed Unapproved Drugs – Compliance Policy Guide, Section 440.100: Marketed New Drugs Without Approved NDAs or ANDAs, which describes FDA's enforcement priorities.

Unapproved Drugs Program, Cont.

The goal of the Unapproved Drugs Initiative is to remove unapproved new drugs from the market and to encourage manufacturers to seek FDA assessment and approval for unapproved products. This initiative is the Agency's risk-based enforcement approach to efficiently and rationally turn all unapproved new drugs into either FDA-approved drugs or drugs that comply with an OTC drug monograph.

Information about the Unapproved Drugs Program is available on the FDA Web site.

Risks of Buying Medicines on the Internet

Many Americans have resorted to the Internet for medical advice and a source for purchasing prescription medicines. While there are many licensed online pharmacies, consumers need to be aware that there are also many unscrupulous marketers ready to take advantage of them through fraudulent online pharmacy Web sites.

The Office of Compliance has an active surveillance and enforcement program aimed at stopping the illegal sale of unapproved drugs on the Internet.

Risks of Buying Medicines on the Internet, Cont.

FDA has a great deal of information on the FDA Web site about the dangers of buying medicines on the Internet. FDA also launched the BeSafeRx national campaign to raise awareness of the dangers of buying prescription medicines from rogue online pharmacies. Buying prescription medicines from rogue online pharmacies can be dangerous. The drugs that are received could be counterfeit, contaminated, expired,

or otherwise unsafe. In addition, rogue online pharmacies may often lack adequate safeguards to protect personal and financial information, and some intentionally misuse the information consumers provide. Therefore, if consumers decide to buy a prescription medicine online, it is important to take certain precautions to ensure they are not being put at risk.

Risks of Buying Medicines on the Internet, Cont.

Quick Tips for Buying Online

- Make sure the Web site requires a prescription. Buy only from U.S. licensed pharmacies located in the United States.
- Verify state licensure of a pharmacy.
- Make sure the Web site has a licensed pharmacist to answer your questions.
- Only provide personal information such as credit card numbers when you are sure the pharmacy is licensed, and the Web site is secure.

For more information, watch the Is Your Online Pharmacy Safe? video.

Importing Prescription Drugs

FDA cannot ensure the safety and effectiveness of products that may have been manufactured under improper conditions. Patients cannot be sure of the identity and purity of such products and these unknowns put patients' health at risk. For these reasons, FDA recommends only obtaining medicines from legal sources in the United States.

The Office of Compliance works with ORA Imports staff to ensure that drugs coming from other countries adhere to FDA's rules and regulations.

Read an FAQ for more information on FDA concerns regarding importation of drug products.

Foreign Drug Manufacturing

Many drug products and active ingredients sold or consumed in the United States are manufactured overseas. These products are required to be manufactured in accordance with FDA regulations and standards, and many also meet other countries' requirements as well. FDA uses several approaches to ensure drug products that are manufactured overseas meet the Agency's requirements and high standards before leaving the exporting country.

Memoranda of Understanding

Negotiated by the FDA, these are agreements that commit governments of exporting countries to ascertain that the products sent to the United States meet U.S. standards.

Inspections

FDA's investigators and analysts inspect foreign facilities that export FDA-regulated products to the United States to make certain that they follow CGMPs and comply with the relevant requirements for ensuring the safety, efficacy, and quality of drugs.

Harmonization of Guidelines and Standards

FDA has taken the lead in founding international organizations that combine the efforts of regulatory authorities and industry associations to harmonize regulatory guidelines for drugs (International Council

on Harmonisation). FDA is also making significant contributions to the efforts of organizations such as Codex Alimentarius, the International Organization for Standardization (ISO), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to raise the standards for food, medical devices, pharmaceuticals, and other regulated products worldwide.

The Mutual Recognition Agreement

The Mutual Recognition Agreement (MRA) between FDA and the European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders.

Drug Supply Chain Threats

Although the U.S. drug supply is one of the safest in the world, the increasingly complex and global nature of the drug supply chain presents unscrupulous entities with multiple opportunities to introduce counterfeit, contaminated, stolen, expired, or improperly stored products into distribution. These products may be unsafe or ineffective and could result in dangerous and even deadly outcomes for patients.

Drug Supply Chain Threats, Cont.

FDA plays a vital role in safeguarding the U.S. drug supply chain against these threats. The Agency's efforts to secure the supply chain include minimizing risks that arise in the supply chain, from the sourcing of a product's ingredients to its manufacture, storage, transit, sale, and distribution. Through these efforts, FDA helps ensure that only safe and effective drugs reach U.S. consumers.

Counterfeit Drugs

Counterfeit drugs raise significant public health concerns because their safety and effectiveness are unknown. A counterfeit drug may contain too much, too little, or none of the active ingredient. It could also be contaminated with dangerous ingredients or contain the wrong active ingredient. Consequently, patients who take counterfeit drugs may not get the treatment that they need and may experience harmful side effects.

FDA uses a multi-layered approach to combat the introduction of counterfeit products into the U.S. drug supply chain. The Agency collaborates with other Federal agencies, pharmaceutical manufacturers, wholesale distributors, retailers, and dispensers to identify counterfeit drugs and prevent them from entering the U.S. drug supply chain. FDA also works with individual countries and regions to combat counterfeit drugs around the world.

Counterfeit Drugs, Cont.

A key component of FDA's anti-counterfeiting efforts is public communication. Through the FDA's Counterfeit Alert Network and other outlets, the Agency is able to alert a wide audience of consumers and health care practitioners to the presence of a counterfeit drug in the market.

FDA's Web site provides a variety of information on the health risks associated with counterfeit drugs and strategies for strengthening the integrity of the drug supply.

Learn more about FDA's approach in combatting counterfeit drugs.

Drug Supply Chain Security

The ability to trace a drug product through the supply chain is a powerful safeguard against the introduction and distribution of substandard, ineffective, and counterfeit drugs.

A robust track-and-trace system can help identify and detect potentially harmful products as they enter the supply chain and can improve the efficiency of product recalls.

The 2013 Drug Supply Chain Security Act (DSCSA) modernized and expanded FDA's authority to require a national system for product tracing and verification.

Drug Supply Chain Security, Cont.

The DSCSA outlines new requirements to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States. To facilitate the development of this system, the DSCSA imposes several new requirements on certain trading partners as defined in the DSCSA.

Product Identification

Manufacturers and repackagers must put a unique product identifier on certain prescription drug packages.

Product Tracing

Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) in the drug supply chain must provide information about a drug covered under the DSCSA and who handled it each time it is transferred between persons in the U.S. market where a transfer of ownership occurs.

Product Verification

Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) must establish systems and processes to be able to verify the product identifier on certain prescription drug packages.

Detection and Response

Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) must quarantine and promptly investigate a drug that has been identified as suspect (such as where there is reason to believe that such product is potentially counterfeit, unapproved, or dangerous).

Notification

Manufacturers, wholesaler drug distributors, repackagers, and many dispensers (primarily pharmacies) must establish systems and processes to notify FDA and other stakeholders if an illegitimate drug is found.

Wholesale Distributor Licensing

Wholesale drug distributors must report their licensing status and contact information to FDA annually, which must then be made available in a public database.

Third-Party Logistics Provider Licensing

Third-party logistic providers must obtain a state or federal license and report their licensure information and name and address of their facility to FDA annually.

Drug Supply Chain Security, Cont.

The DSCSA's provisions, including the requirements just reviewed, will be phased in over a 10-year period starting in 2013. Initially, the product tracing information (such as transaction information, transaction history, and transaction statement) required by the DSCSA may be exchanged in either paper or electronic format.

Furthermore, only lot-level information is required to be exchanged during the phase-in period. By November 2023, however, all product tracing information must be exchanged in a secure, interoperable, electronic manner for the smallest individual saleable unit of a drug product.

Read more information about the DSCSA and its effect on the U.S. drug supply chain security.

Knowledge Check

Question 2

Established in 2013, the _____ Act modernized and expanded FDA's authority to require a national system for product tracing and verification.

a) FDA Amendments

b) Federal Food, Drug, and Cosmetic

c) 21st Century Cures

d) Drug Supply Chain Security

Correct answer feedback: Correct! The correct answer is d. The Drug Supply Chain Security Act was established in 2013 and modernized and expanded FDA's authority to require a national system for product tracing and verification.

Drug Shortages

The primary oversight of drug shortages lies within the CDER Immediate Office. FDA takes great efforts, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations.

The Drug Shortage Staff (DSS) within the CDER Immediate Office work closely with many FDA offices, drug manufacturers, and other stakeholders to help prevent and alleviate drug shortages so that drug products are available for health care professionals and patients.

Access a video about Drug Shortages.

Drug Shortages, Cont.

Once FDA becomes aware of a potential drug shortage, the Agency works with pharmaceutical manufacturers and other stakeholders to manage the shortage.

Expedite assessment of submissions from manufacturers

FDA may expedite assessment of submissions from manufacturers for products that are in shortage or may progress to a shortage. These submissions may be in support of a marketing application for a new product, an NDA or ANDA, or may be in support of manufacturing changes for existing products (for example, a supplemental application for a new manufacturing site).

Help companies to increase manufacturing capacity

FDA may assist drug companies in qualifying additional manufacturing sites or raw material supplies, if those drug companies are interested in increasing manufacturing capacity.

Identify alternative manufacturers of the drug in shortage

FDA may identify alternate manufacturers who can initiate or increase production.

Advise/consult with drug companies

FDA may advise/consult with drug companies on resolution of manufacturing issues.

Explore alternative sources of drug products

In severe shortage situations FDA may look to identify an alternate source of product approved in another country. The manufacturer must be willing and able to temporarily import the product and submit data to the Agency for review to ensuring the drug does not pose undue risks for U.S. patients.

Extend expiration dating of the drug in shortage

If the manufacturer has data to support extension of the expiration dating for the product in shortage, they can submit the data to FDA for review. After acceptable review, FDA is then able to assess the data and approve extended dating to help increase supplies until new production is available. Any new expiry dating will be posted on the CDER Drug Shortages Web page.

Tools to Keep You Informed provides a download for the Drug Shortages Mobile App.

Drug Shortages, Cont.

FDA determines how best to address each shortage situation based on its cause and the public health risk associated with the shortage.

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended the Federal Food, Drug, and Cosmetic Act to require manufacturers to notify FDA of a permanent discontinuance or interruption in manufacture that is likely to lead to a meaningful disruption in the supply of certain prescription drugs that are life-saving, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition.

Shortage notifications and updates may be reported to FDA at drugshortages@fda.hhs.gov.

Search the Drug Shortages Database and sign up for email notifications on information about Drug Shortages which can be found on FDA's Drug Shortages Web page.

Drug Shortages, Cont.

In September 2017, Puerto Rico was impacted by Hurricanes Irma and Maria, category 3 and 4 storms that caused significant damage to an already fractured power grid and health care infrastructure. These

hurricanes devastated the island, leading to shortages of critically important drugs manufactured in facilities in Puerto Rico. The FDA worked with drug manufacturers to address critical shortages of IV fluids aggravated by Hurricane Maria's impact on drug manufacturing facilities in Puerto Rico.

Drug Shortages, Cont.

The FDA closely monitored and identified ways to work with industry to prevent a significant shortfall in production of sodium chloride 0.9% injection in a facility in Puerto Rico. Although these products had been in shortage industry-wide since 2014 and other manufacturers existed, the Agency recognized that further shortage of this product could have a significant impact on public health. The FDA worked with the manufacturer to find solutions to prevent additional shortages, including temporary importation from their foreign facilities. While FDA does not object to the importation of a medically necessary drug from another country, the agency evaluates the foreign companies and drug products to ensure they are of adequate quality and do not pose undo risks to patients.

In addition to not objecting to temporary importation, FDA also worked to expedite the assessment of drug applications to help relieve the shortage.

Registration and Listing Database

The FDA's regulations require that all drug establishments manufacturing drug products, both prescription and over-the-counter, register with the FDA and provide a yearly updated list of all their commercially marketed drug products.

Visit the Drug Establishments Current Registration Site for more information.

Registration and Listing Database, Cont.

FDA maintains a catalog of all drugs in commercial distribution in the United States. FDA's Office of Compliance maintains this database and ensures that drug companies are in compliance with drug registration and listing regulations. FDA relies on this database for administering many key programs, including surveillance inspections, post-marketing safety surveillance, user fee assessments, counterterrorism, monitoring of drug shortages and availability, and determining products that are being marketed without an approved application.

In 2019, FDA took new steps to improve drug supply chain integrity and patient safety by announcing its intention to begin inactivating drug listing records in its database that are improperly listed for among other reasons, the listings are not certified as being active or up-to-date. Drugs with inactivated listing records do not meet the regulatory requirements and persons marketing such drugs or offering them for import into the United States may be subject to enforcement.

National Drug Code (NDC) Number

The end result of this registration and listing process is the assignment of a National Drug Code number, more commonly referred to as an NDC number. The NDC number is a unique 10-digit identifier assigned to drug products that identify the labeler (marketer), the drug product (formulation, dosage form, physical form), and the package size. The NDC number is used to identify and distinguish between different drugs and different strengths or dosage forms of a drug, and is used in billing by public and private health care payors.

It's important to note that an NDC number does not necessarily indicate that a drug is approved.

Access the NDC Directory.

Download the NDC Express Mobile App.

Lesson 2 Summary

Some key points to remember include:

- The Agency has specific enforcement policies that are aimed at efficiently and rationally bringing unapproved drugs into the approval process without imposing undue burdens on the health care system.
- The Office of Compliance has an active surveillance and enforcement program aimed at stopping the illegal sale of unapproved drugs on the Internet.
- The Office of Compliance works to improve the security and integrity of the drug supply chain to protect consumers from receiving counterfeit and substandard drug products.

Lesson 2 Summary, Cont.

Some key points to remember include:

- The Office of Compliance works closely with internal and external stakeholders when a drug company voluntarily removes a potentially dangerous drug product from distribution. FDA strives to address and prevent drug shortages and to keep the public informed.
- FDA is committed to helping manufacturers understand and implement modern quality management techniques and risk management approaches to assure drug quality and availability.

Congratulations! You have successfully completed this lesson!

Module 4: Protection and Promotion of Public Health

Lesson 1: FDA's Role in Emergency Preparedness and Response

Introduction and Learning Objectives

After you complete this lesson, you should be able to:

- Describe FDA's overall role in helping to prepare the nation for naturally occurring and man-made public health emergencies.
- Explain how FDA collaborates with other agencies to support emergency response efforts.
- Identify ways in which FDA plays a role in emergency preparedness and response and in facilitating the development of medical countermeasures.

Introduction

Emergency preparedness and response on a national level require interagency collaborations. FDA works with other Federal agencies to prepare for and respond to public health emergencies.

A few areas of FDA focus include:

- Medical Countermeasures Initiative (MCMi)
- Interagency Collaborations
- FDA's ability to successfully accomplish its mission during emergencies and natural disaster situations

Medical Countermeasures Initiative

FDA's Medical Countermeasures Initiative (MCMi) is an Agency-wide effort to facilitate the development, approval, and availability of drugs, vaccines and other biologic products, diagnostic devices, and other equipment such as ventilators and masks that will be needed to counter exposure to a chemical, biological, radiological, or nuclear (CBRN) threat or an emerging infectious disease threat, such as pandemic influenza. FDA-regulated products used for such purposes are also known as medical countermeasures or MCMs. Scientific staff from FDA's three medical product centers (CDER, CBER, and CDRH) and the FDA's field staff work on developing and testing MCMs, and the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Commissioner provides supportive staff and resources to define and prioritize requirements for MCMs in public health emergencies. This includes coordinating research, setting deployment and use strategies, and facilitating access to MCMs.

Learn more on the MCMi Web site.

Knowledge Check

Question 1

FDA-regulated products used to facilitate the development, approval, and availability of drugs, vaccines and other biologic products, diagnostic devices, and other equipment such as ventilators and masks that will be needed to counter exposure to chemical, biological, radiological, or nuclear threat or an emerging infectious disease threat, such as pandemic influenza are known as:

a) Medical countermeasures (MCMs)

b) Biohazardous tools

c) Biohazardous countermeasures

d) Pandemic preventative measures

Correct answer feedback: Correct! The correct answer is a. Medical countermeasures are FDA-regulated products used to facilitate the development, approval, and availability of drugs, vaccines and other biologic products, diagnostic devices, and other equipment such as ventilators and masks that will be needed to counter exposure to chemical, biological, radiological, or nuclear threat or an emerging infectious disease threat, such as pandemic influenza.

Interagency Collaborations

Although FDA works with Federal agencies with differing missions, the common principle of public health protection is the same. There are many examples of how FDA is working with industry, academia, and other Federal agencies to facilitate the challenge of MCM development, stockpiling, and fielding.

Some examples include:

- Public Health Emergency Medical Countermeasure Enterprise (PHEMCE)
- Filovirus Animal Non-Clinical Group (FANG)

Interagency Collaborations, Cont.

PHEMCE

FDA is a member of the PHEMCE, which coordinates Federal efforts to enhance MCM preparedness for chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases. PHEMCE is led by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and includes the FDA, Centers for Disease Control and Prevention (CDC), and National Institutes of Health (NIH), as well as several other Federal agency partners. FDA continues to work with PHEMCE partners to ensure that the nation is as prepared as possible to deploy MCMs in the event of a public health emergency.

Filovirus Animal Non-Clinical Group

The Filovirus Animal Non-Clinical Group (FANG) is an interdepartmental and interagency collaboration among DoD, FDA, NIH, and CDC that focuses on the advanced development of filovirus MCMs, including therapeutics and vaccines. The FANG focuses on product development tools and development issues related to FDA approval of filovirus MCMs. The FANG also develops consensus recommendations to facilitate standardization of reagents, methods, and procedures across multiple agencies and laboratories.

Knowledge Check

Question 2

FDA is a member of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). Identify PHEMCE's major role:

a) PHEMCE regulates the trade of drugs across international borders.

b) PHEMCE coordinates Federal efforts to enhance MCM preparedness for CBRN threats and emerging infectious disease.

c) PHEMCE approves drug products for medical emergencies.

d) PHEMCE focuses on the advanced development of filovirus MCMs, including therapeutics and vaccines.

Correct answer feedback: Correct! The correct answer is b. Among other responsibilities, PHEMCE coordinates Federal efforts to enhance MCM preparedness for CBRN threats and emerging infectious disease.

FDA's Ability to Meet Its Mission During Emergencies and Natural Disaster Situations

FDA takes an active role in preparing the nation for terrorist events, emerging infectious disease threats, and responses to naturally occurring and man-made public health emergencies. CDER has been involved with preparing for and reacting to public health emergencies such as hurricanes, bioterrorism threats (such as anthrax), radiation accidents, and nerve agent exposures. CDER also works with CBER, CDRH, CVM, and CTP to prepare and respond to emergency situations.

CDER's Role in Emergency Preparedness and Response

Some specific examples of CDER's involvement in emergency preparedness and response include:

- Emergency Use Authorizations (EUA)
- Strategic National Stockpile (SNS)
- Medical Countermeasure Development Under the Animal Rule

- 2015 Drug Subpotency Issue due to Improper Syringe Storage
- Hurricane Emergencies

Emergency Use Authorizations (EUA)

An Emergency Use Authorization (EUA) may only be issued if there is a declaration signed by the Secretary of Health and Human Services. That declaration in turn must be based on a determination of an emergency made by, depending on the circumstances, the Secretary of Homeland Security, Defense, or Health and Human Services, or a finding of a material threat by the Secretary of Homeland Security. The EUA is issued by the FDA to allow during the emergency use of unapproved medical products or unapproved uses of approved medical products to diagnose, prevent, or treat serious or life-threatening diseases or conditions that are caused by CBRN threat agents, or an agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to United States military forces, when there are no adequate, approved, and available alternatives. FDA must find that the product may be effective and that its known and potential benefits outweigh its known and potential risks.

Emergency Use Authorizations (EUA), Cont.

The EUA authority allows FDA to help strengthen the nation's public health protections against CBRN and some military threats by facilitating the availability and use of investigational MCMs needed during public health emergencies.

Atropine Auto-injector EUA

In April 2017, the FDA issued an EUA for the emergency use of an atropine auto-injector for the initial treatment of muscarinic symptoms of poisoning by susceptible nerve agents or certain insecticides (organophosphorus and/or carbamate). This EUA is critical in supporting both American military personnel and first responder preparedness goals for a nerve agent emergency.

COVID-19 Response

During the COVID-19 public health emergency, FDA issued EUAs for certain therapeutic products to be used under the terms specified in the letters of authorization for those products. Each EUA requires that fact sheets providing important product-specific information pertaining to the emergency use under the EUA, including the known and potential risks and drug interactions when using the products to treat COVID-19, be made available to health care providers and patients.

For a list of current EUAs, please visit FDA's Emergency Use Authorization site.

Strategic National Stockpile

The Strategic National Stockpile (SNS), managed by the ASPR, maintains large quantities of medicine and medical supplies to protect the American public if there is a public health emergency (such as a terrorist attack, influenza outbreak, or earthquake) severe enough to cause local supplies to run out.

FDA works closely with Federal partners to support the needs of the SNS. Some examples of how CDER works with the SNS include:

- Regulatory collaboration
- Import/export issues

- Securing adequate MCM supplies
- Supporting the availability and deployment of MCMs

Medical Countermeasure Development Under the Animal Rule

[VIDEO TRANSCRIPT]

FDA has regulations, commonly known as the Animal Rule, that allow FDA to rely on efficacy studies in animals to provide the substantial evidence of the effectiveness needed to support the approval of drugs and the licensure of biological products used to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling CBRN substances when human efficacy studies are not ethical or feasible. The safety of products developed under the Animal Rule is evaluated under existing requirements for drugs or biological products. Fourteen products have been approved or licensed using the Animal Rule, eleven products in CDER and three products in CBER. In general terms, the indications for these MCMs include lethal effects of nerve agent poisoning, cyanide poisoning, pneumonic and septicemic plague, inhalational anthrax, hematopoietic syndrome of acute radiation syndrome, symptomatic botulism, and smallpox.

2015 Drug Subpotency Issue due to Improper Syringe Storage

[VIDEO TRANSCRIPT]

In 2015, FDA's CDER and CDRH were made aware of a loss of drug potency for certain drugs stored in 1 milliliter (mL), 3 mL, 5 mL, 10 mL, 20 mL, and 30 mL general purpose syringes.

Initially, CDER was alerted by the Institute for Safe Medication Practices (or ISMP) that three hospital pharmacies had investigated and reported up to 65% potency loss with two drug products, and possibly other "pH-sensitive" medications when the medications were prepared and then stored in advance of use in certain general purpose syringes.

The company identified a potential interaction between certain drugs, and general purpose syringes that included a certain rubber stopper/plunger and a lubricant that had been submitted as a manufacturing change to the syringes and cleared by CDRH in 2011. No potency loss was associated with the former rubber stopper, which the company continues to use. The general purpose syringes were not cleared by CDRH as container closure devices for storage purposes.

CDER and CDRH worked together and helped to guide the company on educating hospital and compounding pharmacies regarding this issue.

2017 Hurricane Emergencies

[VIDEO TRANSCRIPT]

During FDA's 2017 hurricane response efforts to ensure the safety and quality of drugs, CDER, as part of the FDA Incident Management Group, directed and performed activities such as determining the operating status of firms manufacturing critical drugs, confirming the key logistical needs of these firms, and identifying prioritization criteria for firms that needed federal assistance to resume their manufacturing processes.

CDER assisted in the response to hurricanes Harvey, Irma, and Maria by coordinating the Internet posting of information about a number of issues faced by the displaced Americans, including but not limited to:

- Potential drug shortages caused by damage to local manufacturing facilities
- Facilitating the deployment of medical oxygen via the sea bridge to Puerto Rico
- The safety of medications potentially damaged by flooding or high temperatures
- The safe use of insulin when refrigeration was not available
- The safety of using combination sunscreen and insect repellent in children
- Assisting investigators conducting clinical trials in hurricane-affected areas

Knowledge Check

Question 3

Identify the function of an Emergency Use Authorization (EUA):

a) Focusing on product development tools and development issues related to FDA approval of filovirus medical countermeasures

b) Allowing for the distribution of medical products to sick, disabled, and elderly patients who have been displaced from their homes following a natural disaster

c) Allowing either the use of an unapproved medical product or an unapproved use of an approved medical product during certain types of emergencies with specified CBRN agents or agents that may cause an imminently life-threatening and specific risk to U.S. military forces when there are no adequate, approved, or available alternatives

d) Prohibiting interstate commerce in misbranded and adulterated food and drug products

Correct answer feedback: Correct! The correct answer is c. An Emergency Use Authorization allows either the use of an unapproved medical product or an unapproved use of an approved medical product during certain types of emergencies with specified CBRN agents or agents that may cause an imminently life-threatening and specific risk to U.S. military forces when there are no adequate, approved, or available alternatives.

CDER's Role in Emergency Preparedness and Response

CDER contributes to the development and currency of the information posted on FDA's emergency preparedness and response Web page (also available through www.fda.gov). This includes information about:

- Drugs that may be used to reduce or prevent the effects of exposure to CBRN threat agents or to emerging infectious diseases.
- Information about EUAs, whereby FDA may allow investigational MCMs to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN agents or agents that may cause an imminently life-threatening and specific risk to U.S. military forces, when certain statutory criteria are met.

- The safe use of medical products during a natural disaster, such as what to do with medicines exposed to flood water or medicines that cannot be refrigerated during a power outage from a hurricane (e.g., insulin).

CDER's Role in Emergency Preparedness and Response, Cont.

Emergency Preparedness - Drugs

Emergency Preparedness and Response

Lesson 1 Summary

Some key points to remember include:

- Emergency preparedness and response on a national level require interagency collaborations.
- CDER and other FDA medical product centers work together with other federal agencies to prepare for and respond to public health emergencies.
- CDER and other FDA medical product centers take an active role in helping prepare the nation for terrorist events, emerging health threats, and responding to public health emergencies and natural disasters.
- CDER posts useful information regarding emergency preparedness and response on www.fda.gov.

Congratulations! You have successfully completed this lesson!

Lesson 2: International Engagement and Response

Introduction and Learning Objectives

After completing this lesson, you should be able to:

- Describe the efforts and outcomes of the International Council for Harmonisation (ICH).
- Describe FDA's strategy to address the complex issues posed by globalization.
- Describe how FDA foreign offices protect the safety of the American people.

International Engagement and Response

To fulfill its mission to monitor and ensure the safety of the supply chain for food, feed, medical products, cosmetics, and tobacco products that enter the United States from other parts of the world, the FDA engages in partnerships with foreign governments, regulatory coalitions, development organizations, academic institutions, among others.

International Council for Harmonisation (ICH)

The ICH was established in 1990 to bring together government regulators and drug industry representatives from the United States, the European Union, and Japan to promote a more efficient and uniform drug regulatory process. In 2015, ICH was reformed to establish the Association as a true global initiative that expands beyond the founding members by creating a pathway for more regulators and industry associations from around the world to join. These efforts help make new drugs available, with minimum delays, to both American consumers and those in other countries. This unique initiative is focused on reducing duplicative testing conducted during the research and development of new medicines.

International Council for Harmonisation (ICH), Cont.

Since the ICH program's initiation, efforts to harmonize have successfully:

- Reduced regulatory time burden for the assessment of new applications by establishing a Common Technical Document for regulatory submissions in member countries
- Established common requirements for preclinical animal testing for biotechnology products, clinical trials to establish safety and efficacy of new molecular entities, and chemistry, manufacturing, and controls information for these products
- Saved time and money for industry by reducing the human resources required to change formats for submission among international drug regulatory authorities
- Increased patient access to medicines globally

Knowledge Check

Question 1

One of the successful efforts of the International Council for Harmonisation (ICH), since its initiation in 1990 and its reformation in 2015, was:

a) Saving time and money for industry by reducing the human resources required to change formats for submission among international drug regulatory authorities.

b) Assisting CDER in preparing for and reacting to public health emergencies.

c) Assisting CBER and CDRH to prepare and respond to emergency situations.

d) Collaborating with the Public Health Emergency Countermeasure Enterprise to develop additional MCMs.

Correct answer feedback: Correct! The correct answer is a. One of ICH's successful efforts was saving time and money for industry by reducing the human resources required to change formats for submission among international drug regulatory authorities.

International Council for Harmonisation (ICH), Cont.

Global production of FDA-regulated products has quadrupled over the last decade and continues to grow. As globalization alters the economic and security landscape, FDA must change the way it fulfills its mission. FDA has established international offices and posted staff in strategic locations around the world including China, Europe, India, and Latin America. FDA's international staff work closely with their national and regional regulatory counterparts and with other U.S. government agencies stationed abroad to perform functions essential to FDA's ability to protect U.S. consumers.

Learn more about FDA's Global Initiative.

Globalization Challenges

FDA faces ever-greater challenges in determining whether a product has been properly manufactured, distributed, and stored and even in determining who has handled the product. The manufacture of a single product can now involve multiple parties from different countries engaged at various steps throughout the process. Along the way, there are opportunities for the product to be improperly formulated, packaged, contaminated, diverted, counterfeited, or adulterated.

Globalization Challenges, Cont.

FDA has mobilized diverse approaches as part of its strategy to address the complex issues posed by globalization, including efforts to:

- Develop new enforcement and regulatory tools
- Conduct more foreign inspections
- Increase collaboration with foreign regulators and other stakeholders
- Develop internationally harmonized standards and standards convergence
- Educate foreign industry about FDA requirements
- Increase transparency and accountability in the supply chain

Learn more about FDA and Globalization.

International Collaboration and Drug Recalls

CDER's international office coordinates on a daily basis with international regulatory authorities to share and exchange regulatory information in the following capacities:

- Sharing drug review assessments and reports
- Sharing safety alerts and signals
- Coordinating with international counterparts on drug shortage issues
- Providing clarity and interpretation of FDA guidance and policy to international organizations
- Sharing public and nonpublic information, as appropriate, with international public health authorities through FDA's established confidentiality commitments
- Coordinating international meetings and teleconferences for CDER experts
- Coordinating CDER-originated information requests to external regulatory authorities

International Collaboration and Drug Recalls, Cont.

Regarding drug recalls, in the summer of 2018, FDA learned and reported that a common active pharmaceutical ingredient (API) for some generic versions of a class of drugs called angiotensin II receptor blockers (ARBs) contained nitrosamine impurities that did not meet the agency's safety standards. ARBs, including valsartan, irbesartan, losartan, and others, are a class of medicines used to treat high blood pressure and heart failure. The nitrosamine impurities are known environmental contaminants and found in water and foods, but they are probable human carcinogens and their presence in drug products is not acceptable.

FDA worked in collaboration with the European Medicines Agency (EMA) and other regulators to address this important drug safety issue. The agency immediately undertook a major operation to investigate and to identify the root causes for the presence of these impurities in some ARB drugs and to work with companies to address the risks that the impurities pose to patients.

International Collaboration and Drug Inspections

The Mutual Recognition Agreement (MRA) between the United States and European Union allows drug inspectors to rely upon information from each other's drug manufacturer inspections. Under the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in 2012, FDA has the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determines those authorities to be capable of conducting inspections that meet U.S. requirements.

FDA and the EU have collaborated since May 2014 to evaluate the way they each inspect drug manufacturers and have determined that an MRA will:

- Yield greater efficiencies for U.S. and EU regulatory systems by avoiding duplication of inspections
- Enable reallocation of resources towards inspection of drug manufacturing facilities with potentially higher public health risks across the globe
- Leverage expertise of drug inspectors
- Allow for enhanced communication, coordination, and collaboration to respond more quickly to emerging public health risks

Knowledge Check

Question 2

Identify one of the capacities CDER's international office coordinates on a daily basis to share and exchange regulatory information:

a) Approving drug products in foreign countries

b) Providing clarity and interpretation of FDA guidance and policy to international organizations

c) Exchanging chemical compounding information for drug products needed but not yet available in other countries

d) Providing review and feedback on FDA regulatory changes for the United States

Correct answer feedback: Correct! The correct answer is b. CDER coordinates with international offices on a daily basis to share and exchange regulatory information by providing clarity and interpretation of FDA guidance and policy to international organizations.

Knowledge Check

Question 3

Identify a region in which FDA has **not** yet established an international office:

a) Latin America

b) China

c) India

d) Australia

e) Europe

Correct answer feedback: Correct! The correct answer is d. FDA has not yet established an international office in Australia.

Lesson 2 Summary

Some key points to remember include:

- The FDA faces challenges in determining whether a product has been properly manufactured, distributed, and stored and even in determining who has handled the product.
- The FDA engages in partnerships with foreign governments, regulatory coalitions, development organizations, academic institutions, among others to fulfill its mission.
- The FDA works globally to promote and protect public health and address the challenges posed by globalization through engagement with trusted partners and strategies to enhance use of resources.

Congratulations! You have successfully completed this lesson!

Lesson 3: Patient Engagement, Cross Agency Engagement, Communications, and Advertising

Introduction and Learning Objectives

Stakeholder engagement continues to play a more prominent role in our work and has expanded significantly in the past 10 years. The agency communicates with our regulatory counterparts in other countries, with patient advocacy groups, health care professional organizations, and individual patients. CDER also monitors prescription drug advertising to ensure that what is communicated is truthful and balanced.

After completing this lesson, you should be able to:

- Describe how FDA facilitates engagement with patients and advocacy groups.
- Identify activities to enhance the safe use of drug products that involve a collaboration among FDA and other agencies and organizations.
- Identify means by which FDA communicates information to promote and protect public health.
- Describe how CDER oversees drug product advertising to ensure that proper benefit and risk information of FDA-regulated products is conveyed to the American public.

Communications – External and Expanded Collaborative Initiatives

In 1991 the FDA began including patient perspectives in Advisory Committee meetings. Since then FDA has established additional public engagement collaboratives such as the:

- EMA working group on patient engagement to share best practices involving patients' needs.
- Clinical Trials Transformation Initiative created the Patient Engagement Collaborative (PEC) to provide an ongoing forum to discuss how to achieve more meaningful patient engagement in medical product development and other regulatory discussions.
- Cross-Center Patient Council is designed to bring together all FDA medical product Centers and Offices to better coordinate and integrate the role of patient perspectives in regulatory decision-making over the total product lifecycle.
- Patient Affairs Staff (PAS), in the Office of the Commissioner, is devoted to improving, expanding, and sustaining communication with patients and their community and lead cross-center initiatives.

- Professional Affairs and Stakeholder Engagement (PASE), in CDER, strives to inspire and promote a culture of two-way engagement to enhance drug development and safety.
- Patient-Focused Drug Development program works to enhance the incorporation of patient input in drug development and evaluation.

Patient Affairs Staff (PAS)

FDA's Patient Affairs Staff (PAS) work to improve, expand, and sustain communication with patients and their community. They help educate patients, patient advocates, and their health care professionals about medical product regulations and continue to look at ways to involve patients more effectively in regulatory decisions related to medical product safety and approval.

Request to Connect

Email: patientaffairs@fda.gov

Patient Affairs Staff (PAS), Cont.

PAS:

- Creates public-private collaborations and partnerships
- Leads cross-cutting programs and activities that leverage best practices and enhance patient engagement
- Enhances FDA's external communication platforms for bi-directional communication

Learn more about PAS on our Web site and through this video.

Knowledge Check

Question 1

FDA's Patient Affairs Staff (PAS) is responsible for:

a) Providing direct patient advocacy in a hospital setting.

b) Educating patients, patient advocates, and their health care professionals about medical product regulations.

c) Providing education to health care professionals on the proper usage of approved drugs.

d) Conducting clinical trials.

Correct answer feedback: Correct! The correct answer is b. PAS is responsible for educating patients, patient advocates, and their health care professionals about medical product regulations.

Patient Engagement and PASE

Engagement

Creates and facilitates public and private collaborations within the health care community by serving as a neutral convener and liaison for external (private and public) stakeholders regarding initiatives that are of interest to CDER. Provides systematic and coordinated engagement with stakeholders to develop complementary, collaborative actions that will improve medication use and increase awareness of

regulatory activities. This includes meeting with and responding to advocacy groups and professional organizations about drug development, drug assessment, and drug safety.

PASE uses different channels to engage the stakeholders, such as:

- CDER's new External Stakeholder Meeting Request (ESMR) system, launched in February 2018. This system provides external, non-industry stakeholders a focal point to request meetings with CDER on drug development and drug safety matters. To submit a meeting request on drug-related topics, please visit Request a Meeting on Drugs.
- Network of Experts (NoE) Program: The NoE aims to facilitate exchange of information between CDER staff and a network of individuals (Experts). The NoE is a vetted network of organizations including clinicians, scientists, and engineers who provide CDER staff with supplemental knowledge and rapid access to up-to-date best practices and clinical experience for safe management of patients in various clinical settings and facilities.
- Stakeholder Outreach: PASE supports, promotes, and amplifies CDER campaigns, initiatives, and messages through targeted stakeholders via listserv messages and phone calls.

Drug Trials Snapshots

Creates and publishes the Drug Trials Snapshots that provide consumers and health care professionals with concise information about who participated in clinical trials that supported the FDA approval of new drugs. The information in the Snapshots also highlights where the trials were conducted and whether there were any differences in the benefits and side effects among different demographic groups.

Safe Use Initiative

Engages, leverages, and supports the public and private sector in collaborative efforts to address issues of interest to CDER, including preventable medication harm and/or safe medication use issues. Safe Use works to reduce preventable harm from medication misuse, abuse, and errors.

For more information, visit the PASE Web site.

Patient Engagement and PASE - Safe Use Activities

The Safe Use Initiative partners with other organizations to enhance the safe and appropriate use of FDA-regulated drugs. Through the Safe Use Initiative, FDA is building public and private coalitions throughout the health care community in order to identify workable solutions for reducing and, where possible, eliminating preventable harm from drugs.

The mission of the Safe Use Initiative is to create and facilitate public and private collaborations within the health care community.

Our partners in Safe Use may include:

- Federal agencies
- Pharmacies, hospitals, and other health care entities
- Patients, caregivers, consumers, and their representative organizations
- Health care professionals and professional societies

For additional information, visit the Safe Use Initiative's Web site.

Patient Engagement and PASE - Safe Use Activities, Cont.

Improving the Safe Use of Fluoroquinolones

[VIDEO TRANSCRIPT]

In 2016, FDA removed three common indications for using fluoroquinolone antibiotics: sinusitis, uncomplicated urinary tract infection, and acute exacerbation of chronic bronchitis. FDA took this action because there are other antibiotics available that do not have the serious side effects of the fluoroquinolones. The Safe Use Initiative funded a project to increase awareness of these changes and to study the effect of providing feedback about prescribing practices to individual physicians.

This project identified high prescribers of fluoroquinolone antibiotics by matching Medscape subscribers to individual- level prescribing data. These frequent prescribers were then sent their prescribing data compared to same specialty peers, information on FDA labeling updates, or both. A CME component was also available. Prescribers exposed to the interventions reduced prescribing by 8.5% compared to controls. Those exposed to both the intervention component and the CME achieved a 21.7% reduction. As a result, an estimated 85,484 fewer fluoroquinolone prescriptions were written during the study.

Pragmatic Risk Score to Identify Patients at Risk of Severe Hypoglycemia

[VIDEO TRANSCRIPT]

Patients with Type 2 diabetes are treated with medications to lower their blood sugar to normal levels. However, these medications sometimes lower blood sugar too much, causing serious side effects. These side effects can include feeling dizzy, confusion, and even passing out. Serious episodes of low blood sugar can lead to devastating injuries. Health care providers could address these risks more effectively if they were able to predict which patients are most likely to experience serious problems from low blood sugar.

In this project, researchers developed and validated a 6-question tool that can identify those patients at highest risk (incidence >5% per year, or 2% of population) from those at lowest risk (incidence <1%, or 87.3% of population). The initial study utilized ICD-9 codes and was re-validated using ICD-10. Using this tool, any health care provider can quickly identify high-risk patients and take measures to prevent these side effects and injuries. Results were published in the Journal of the American Medical Association Internal Medicine and Diabetes Care.

Knowledge Check

Question 2

Which FDA initiative aims to enhance the safe and appropriate use of FDA-regulated drugs?

a) Safe Use Initiative

b) Patient Affairs Staff

c) Professional Affairs and Stakeholder Engagement

d) Drug Trial Snapshots

Correct answer feedback: Correct! The correct answer is a. The Safe Use Initiative aims to enhance the safe and appropriate use of FDA-regulated drugs.

Patient-Focused Drug Development

Patient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation.

Patient-Focused Drug Development, Cont.

FDA's PFDD efforts include:

- The development of a methodological guidance series to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decision making.
- A pilot grant program to support the development of publicly available core set(s) of clinical outcome assessments (COAs) and their related endpoints for specific disease indications.
- FDA-led PFDD meetings to directly hear patients' perspectives on specific diseases and their currently available treatments.
- Externally-led PFDD meetings, where external groups host their own PFDD meetings using FDA-led PFDD meetings as a model.

To learn more about these PFDD efforts and others, please visit CDER's PFDD Homepage.

Patient-Focused Drug Development, Cont.

These efforts and others to facilitate the incorporation of patient input into decision-making are led by the Patient-Focused Drug Development Program Staff in CDER's Office of the Center Director. To learn more about the PFDD Program Staff, please visit the PFDD Program Web site.

Prescription Opioid Painkillers

Prescription opioids are powerful, pain-reducing medicines that can help patients successfully manage pain when prescribed and used properly. When misused or abused, however, these drugs can cause serious harm, including addiction, overdose, and death. One of the highest priorities of the FDA is advancing efforts to address the crisis of misuse and abuse of opioid drugs harming families. The approach to reducing the misuse and abuse of opioids is outlined in FDA's 2018 Strategic Policy Roadmap, which addresses various facets of this complex issue and sets forth FDA's four key priorities.

Decrease Exposure & Prevent New Addiction

Reducing the number of Americans who are addicted to opioids and cutting the rate of new addiction is one of the FDA's highest priorities. This may be achieved by ensuring that only appropriately indicated patients are prescribed opioids and that the prescriptions are for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place.

Support Treatment of Those with Opioid Use Disorder

Given the scale of the opioid crisis, with millions of Americans already affected, prevention is not enough. More must be done to facilitate treatment options and the development of therapies to address opioid use disorder (OUD) as a chronic disease with long-lasting effects. This includes helping more people secure medication-assisted treatment (MAT).

MAT refers to the use of medications in combination with counseling and behavioral therapies that is effective in the treatment of OUD and can help some people to sustain recovery.

Read more about Opioids and MAT on the FDA Web site.

Foster Development of Novel Pain Treatment Therapies

FDA is taking steps to help those with acute and chronic pain who need access to medicines, including opioids, get improved treatment alternatives. To that end, FDA supports the development of opioids with abuse-deterrent properties. While these innovative formulations are designed to make it harder for people to manipulate the opioid drug so it can't be abused, it's important that prescribers and patients understand that these drugs are not "abuse-proof," and they do not prevent addiction, overdose, or death. FDA also supports the development of novel non-opioid therapies (including drugs, devices, and biologics) that could eventually replace or at least reduce the need for opioids.

Improve Enforcement & Assess Benefit/Risk

The FDA plays an enforcement role when it comes to the illicit market for diverted opioids and illegal drugs, including collaborating with Customs and Border Protection on interdiction work on drugs being shipped through the mail. Many of the illicit drugs brought into the United States, including products laced with potentially lethal doses of fentanyl, are being purchased online and shipped in the mail. Although the sale of prescription opioids without a valid prescription is illegal, the FDA continues to see these products in the packages we inspect.

Find videos and information about the serious dangers of keeping unused opioid pain medicines in the home and the safe disposal of these medicines.

Learn more about opioid medicines on the FDA Web site.

Communication Platforms

FDA communicates regularly with all of our stakeholders. When new drugs are approved or if new safety information is discovered, whether it is emerging or confirmed, it is important that FDA shares new information with the health care community, patients, and consumers.

FDA uses a number of electronic communication channels to inform the public about emerging safety information and to educate health care professionals and consumers about the critical importance of monitoring for and reporting adverse events and problems to FDA and manufacturers.

Let's review a few of the different channels of communication FDA uses.

Social Media – Twitter, Facebook, and LinkedIn

FDA provides timely drug information on new drug approvals, safety alerts, compliance actions, and consumer information with a link for more information. Find information at Twitter | Facebook | LinkedIn.

RSS Feed

RSS (Really Simple Syndication) news feeds make it possible for you to put together your own customized list of news and information. Thousands of Web sites, including FDA's, have started adding special code that allows RSS news readers (also called RSS aggregators) to pick up the content. Then, the next step is to sign up with a news reader and choose the sites from which you want to receive news. Visit Tools to Keep You Informed to learn more.

Email Alerts and Listservs

Our free e-mail alert service allows you to receive important FDA news and information as they become available. Sign up to receive updates by visiting the Get Email Updates Web site. Scroll down to 'Drugs' and select the topics that are of interest. Sample groups include CDER Drug Safety Labeling Changes, CDER NEW, Drug Information, Generic Drugs Updates, Compounding, and more.

FDA Drug Info Rounds

FDA Drug Info Rounds are a series of training videos for practicing clinical and community pharmacists. Drug Info Rounds are brought to you by pharmacists in the Office of Communications (OCOMM), Division of Drug Information (DDI). Pharmacists in DDI answer hundreds of questions every day about drug products and FDA actions. The goal of the FDA Drug Info Rounds program is to provide important and timely drug information to pharmacists so they can help patients make better medication-related decisions. Watch the FDA Drug Info Rounds videos to learn more.

Audio Podcasts

The FDA Drug Safety audio podcasts program for health care professionals provides an opportunity to download a summary of emerging safety information about drugs in conjunction with the release of Drug Safety Communications and other drug safety issues. Visit the FDA Drug Safety Podcasts Web site to learn more.

Public Education Campaigns

Public education campaigns are another way that FDA educates the public. Some public education campaigns include:

- Generic Drugs
- Biosimilars
- Safe Opioid Disposal

Knowledge Check

Question 3

How can consumers receive timely updates on new drug approvals, safety alerts, compliance actions, and consumer information?

a) The Drug Information listserv

b) Google

c) FDA's physical newsletter

d) FDA's weekly podcast

Correct answer feedback: Correct! The correct answer is a. Consumers can find timely drug information on new drug approvals, safety alerts, compliance actions, and consumer information by signing up for the Drug Information listserv.

Drug Product Promotion and Marketing and Advertising Review

One last core activity under CDER oversight is drug product promotion. The Office of Prescription Drug Promotion (OPDP) regulates prescription drug promotion and advertising to ensure that product communications and information provided by, or on behalf of, drug companies are truthful, balanced, and accurate. OPDP has comprehensive surveillance, enforcement, and educational programs designed to improve product labeling and promotional information communicated to health care professionals and consumers.

Drug Product Promotion and Marketing and Advertising Review (Monitoring Pharma)

OPDP staff engage in a variety of tasks to perform their responsibilities, including:

- Providing written comments to pharmaceutical companies on proposed promotional materials to ensure clear and unambiguous communication of the laws and regulations relating to prescription drug promotion
- Reviewing complaints about alleged promotional violations
- Initiating enforcement actions on promotional materials that are false or misleading
- Comparing the product labeling and promotional materials of various closely related products to ensure that the regulatory requirements are consistently and equitably applied
- Traveling to major medical meetings and pharmaceutical conventions to monitor promotional exhibits and activities
- Serving as the expert on advertising and promotional issues for CDER

Drug Product Promotion and Marketing and Advertising Review (Monitoring Pharma), Cont.

OPDP regulates the following types of promotion:

- Sales representative presentations
- Company-sponsored speaker presentations
- TV and radio advertisements
- All written or printed prescription drug promotional materials

OPDP does NOT regulate promotion of:

- Over-the-counter drugs
- Dietary supplements
- Medical devices

The Federal Trade Commission (FTC) regulates the advertising of OTCs and dietary supplements.

CDRH regulates the advertising of medical devices.

The Bad Ad Program - Truthful Prescription Drug Advertising and Promotion

FDA has implemented the "Bad Ad" program, which is designed to educate health care professionals about the role they can play in helping the Agency make sure that prescription drug advertising and promotion is truthful and not misleading.

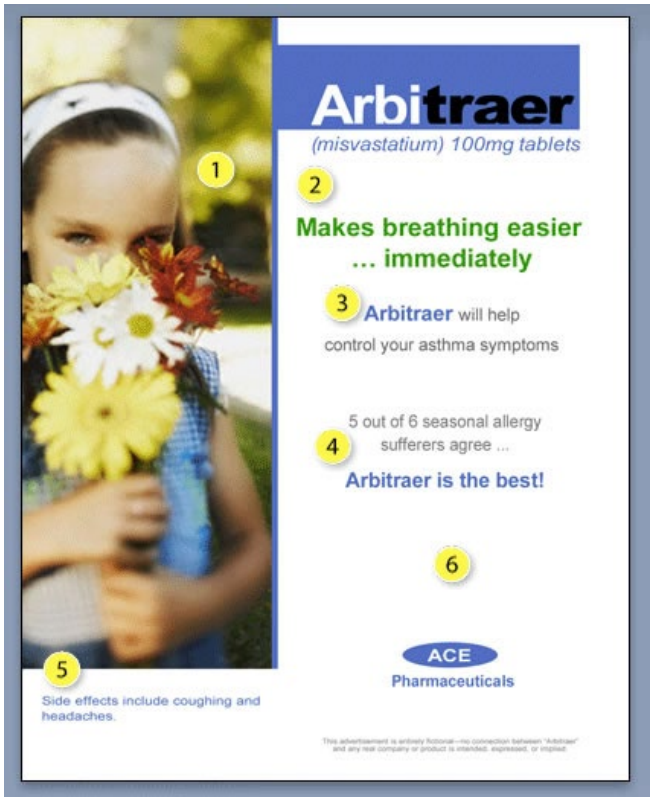
The prescriber can play an important role in ensuring that prescription drug advertising and promotion is truthful by **recognizing** and **reporting** misleading drug advertising and promotion.

Learn more about the Bad Ad program.

The Bad Ad Program - Truthful Prescription Drug Advertising and Promotion: Recognize

Be aware of the many advertisements and promotions that you see every day.

1. The image of the young girl in the ad is misleading because the fictional drug is approved for use only in adults 18 years of age and older.
2. Although claims generally must be supported by data from well-designed studies, consumers may not know if such studies exist or what they show. If FDA determines that claims are false or misleading, it will take action to have the ad discontinued. In the short term, if you have doubts about a claim in an advertisement, you should talk to your health care provider.
3. This ad falsely states that Arbitraer is approved to help control asthma symptoms. This fictional drug (see the Correct Product Claim Ad) is approved to treat seasonal nasal allergy symptoms.



Alternative Text: Example of advertisement, Arbitraer. Young girl holding a bouquet of flowers partially covering her face marked "1". Arbitraer (misvastatium) 100 mg tablets. 2. Makes breathing easier…

immediately. 3. Arbitraer will help control your asthma symptoms. 5 out of 6 seasonal allergy sufferers agree… 4. Arbitraer is the best! 5. Side effects include coughing and headaches. 6. ACE Pharmaceuticals.

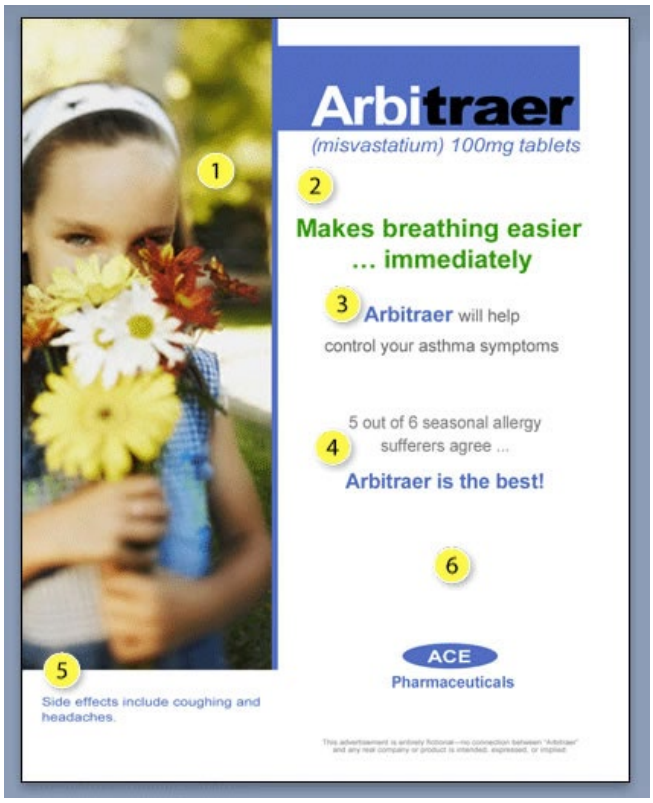
The Bad Ad Program - Truthful Prescription Drug Advertising and Promotion: Recognize, Cont.

The other problems with this ad are:

4. This ad presents Arbitraer's risks in small-size type and positions this information far from where the benefits are discussed, so it is harder for the reader to notice and read the risks. "Fair balance" requires that risks must be presented with prominence and readability reasonably comparable to the presentation of the benefits.

5. The ad does not include the "brief summary," which includes additional required risk information. The law requires that ads include this "brief summary." Also, the ad does not include the statement, "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088." This statement is required to be included in print ads by the Food and Drug Amendments Act of 2007.

Access additional examples and learn more about truth in prescription drug advertising and promotion on the Sample Prescription Drug Advertisements Web site.



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The Bad Ad Program - Truthful Prescription Drug Advertising and Promotion: Report

Help FDA stop violations by reporting activities and messages that you consider false or misleading.

How to Report:

Phone: 855-RX-BADAD

(855-792-2323)

E-Mail: BadAd@fda.gov

Write: FDA/CDER/OPDP

5901-B Ammendale Rd,

Beltsville, MD 20705-1266

Fax: 301-847-8444

Knowledge Check

Question 4

Which of the following does OPDP **not** regulate promotion of?

a) Sales representative presentations

b) TV and radio advertisements

c) Dietary supplements

d) Company-sponsored speaker presentations

Correct answer feedback: Correct! The correct answer is c. OPDP does not regulate the promotion of dietary supplements.

Lesson 3 Summary

Some key points to remember include:

- FDA staff help educate patients, patient advocates, and health care professionals about medical product regulations and continue to look at ways to involve patients more effectively in regulatory decisions related to medical product safety and approval.
- The mission of the Safe Use Initiative is to create and facilitate public and private collaborations within the health care community.
- One of the highest priorities of the FDA is advancing efforts to address the crisis of misuse and abuse of opioid drugs harming families.

Lesson 3 Summary, Cont.

Some key points to remember include:

- FDA uses a number of electronic communication channels to inform the public about emerging safety information and to educate health care professionals and consumers about

the critical importance of monitoring for and reporting adverse events and problems to FDA and manufacturers.
- FDA regulates the advertising of prescription drug products to ensure that prescription drug information provided by drug companies is truthful, balanced, and accurately communicated.

Congratulations! You have successfully completed this lesson!

Course Conclusion

Thank you for completing this overview on FDA's regulatory oversight of drug and biological products.

We hope that the course provides a better understanding of FDA's, and more specifically CDER's, role in the regulation of drug development, marketed drugs, quality testing, and post-market surveillance, along with FDA's role in emergency preparedness and response.

Course Conclusion, Cont.

You should now be able to:

- Describe and explain the drug development and review process in the United States for new drugs, generics, OTC drugs, and biosimilars
- Outline CDER's role in post-marketing safety surveillance for medical products
- Identify ways CDER disseminates safety information about medical products to both health care professionals and their patients
- Describe FDA and CDER initiatives and commitments for the protection of public health