Policy, Practice, and Regulatory Issues

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Learning Objectives

1. List the congressional committees and government agencies that regulate health care in the United States.
2. Identify the regulatory and oversight bodies with jurisdiction over health system delivery of care.
3. Explain recent federal legislative and regulatory activity that affects the delivery of health care.
4. Describe the regulatory actions that govern the prescription drug approval process and the conduct of human subjects research.
5. Describe national quality initiatives aimed at improving health care delivery and patient health outcomes.
6. Explain medication policy implications at an institutional level.

Abbreviations in this Chapter

ACA	Patient Protection and Affordable Care Act of 2010
ANDA	Abbreviated new drug application
CFR	Code of Federal Regulations
DQSA	Drug Quality and Security Act of 2013
ETASU	Elements to Assure Safe Use
FD&C Act	Food, Drug, and Cosmetic Act of 1938
HEDIS	Healthcare Effectiveness Data and Information Set
HIPAA	Health Insurance Portability and Accountability Act of 1996
HITECH	Health Information Technology for Economic and Clinical Health Act
INDA	Investigational new drug application
IRB	Institutional review board
MACRA	Medicare Access and CHIP Reauthorization Act of 2015
MUE	Medication use evaluation
NDA	New drug application
PHI	Protected health information
PSO	Patient safety organization
REMS	Risk Evaluation and Mitigation Strategies

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Which congressional committee is responsible for deciding how much funding the National Institutes of Health (NIH) receives as part of the 21st Century Cures Act?
   A. House and Senate Appropriations.
   B. House Energy & Commerce.
   C. Senate Health, Education, Labor and Pensions (HELP).
   D. House Ways & Means.

2. Which of the following health care practices is not regulated by the Department of Health and Human Services (DHHS) or one of its agencies?
   A. Research involving human subjects.
   B. Health Insurance Portability and Accountability Act of 1996 (HIPAA) provisions to protect identifiable health information.
   C. The diversion of controlled substances.
   D. Inspection of drug manufacturers for compliance and good manufacturing processes.

3. The Drug Quality and Security Act (DQSA) of 2013 differentiated a traditional compounder from an outsourcing facility. Which of the following characteristics is unique to traditional compounders?
   A. Subject to U.S. Food and Drug Administration (FDA) registration and inspection
   B. Required to follow good manufacturing practices for compounding
   C. Compounded for identified individual patient
   D. Exempt from track-and-trace requirements

4. Which is the best description of the Safe and Secure Drug Disposal Act of 2010?
   A. Authorizes hospitals and clinics with on-site pharmacies and retail pharmacies to become collectors.
   B. Authorizes DHHS to promulgate rules for patient disposal of unused controlled substances.
   C. Requires all collectors to register as reverse distributors.

D. Requires current Drug Enforcement Administration (DEA) registrants to become collectors.

5. The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 includes which of the following provisions?
   A. Establishment of alternative payment models and a merit-based incentive payment system.
   B. Provision of a financial incentive to eligible professionals and eligible hospitals to begin the "meaningful use" of electronic health records.
   C. Creation of an optional Medicaid State Plan benefit allowing states to establish Health Homes for Medicaid patients with chronic conditions.
   D. Creation of the Centers for Medicare and Medicaid Services (CMS) Innovation Center to pioneer novel care delivery and payment models

6. Which option correctly describes when an Investigational New Drug Application (INDA) should be submitted to the FDA?
   A. Before preclinical studies.
   B. After preclinical studies but before phase I clinical trials.
   C. During phase II studies.
   D. After phase III studies but before market approval.

7. Which of the following statements regarding generic drugs and their approval process is true?
   A. New Drug Applications (NDAs) for generic drugs are submitted to FDA's Center for Drug Evaluation and Research after 3–5 years of market exclusivity.
   B. Drug manufacturers are required to demonstrate therapeutic equivalence in an Abbreviated New Drug Application (ANDA) for a generic drug.
   C. Once approved, the generic and brand manufacturers retain a 90-day exclusivity period.
   D. An authorized generic is produced by the brand company under the NDA but marketed as a generic.

8. Regarding the evaluation of medications for interchange in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), which statement is most accurate?
   A. Products with an A rating are pharmaceutical equivalents only and may not be interchanged.
   B. Interchangeable products may vary in dosage form and route of administration.
   C. Products with an A rating are pharmaceutical equivalents and bioequivalents and may be interchanged.
   D. Interchangeable products may vary in their release mechanism or excipients.

9. With respect to reporting for adverse drug experiences, which is the best option to correctly describe the purpose of MedWatch Form FDA 3500A?
   A. It is for voluntary reporting by health care professionals of a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement.
   B. It is for consumer reporting of adverse drug experiences.
   C. It may contain patient identifiers and still comply with the HIPAA Privacy Rule.
   D. It is the form that must be submitted by investigational new drug (IND) reporters, manufacturers, distributors, importers, and facility personnel.

10. Which situation best represents an adverse drug event that should be reported to the FDA Adverse Event Reporting System (FAERS)?
    A. A warfarin order dispensed to the wrong patient.
    B. Hemorrhage caused by heparin use.
    C. Hospitalization of a patient caused by an error in the insulin dose on a prescription.
    D. Development of hives in a patient taking cephalexin.

11. Which option best describes the development and maintenance of quality measures?
    A. The Joint Commission is responsible for developing and maintaining the Healthcare Effectiveness Data and Information Set (HEDIS).
    B. The Patient-Centered Outcomes Research Institute (PCORI) developed the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey.
    C. The National Quality Forum (NQF) is responsible for assessing and endorsing quality standards.
    D. The National Committee for Quality Assurance (NCQA) is responsible for developing and maintaining the National Hospital Quality Measures.

12. Which of the following options correctly describes research involving the comparison of two FDA-approved antihypertensive agents in older adult outpatients?
    A. It would be governed by Code of Federal Regulations (CFR) regulations at Title 21 Part 56.
    B. It would be governed by CFR regulations at Title 45 CFR Part 46.
    C. It would be exempt from institutional review board (IRB) review.
    D. It would require either written authorization or a waiver of authorization to utilize PHI for research use.

13. Which statement regarding institutional review board (IRB) review of research is most accurate?
    A. Research involving no more than minimal risk, and minor changes made to approved research protocols, may be considered exempt from IRB review.
    B. Use of de-identified information or limited data sets requires a personal health information (PHI) waiver of authorization.
    C. Waivers of informed consent will be considered if the research involves investigations in high-risk populations for whom limited treatments exist.
    D. Research conducted in established or commonly accepted educational settings involving normal educational practices requires IRB review.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination:
Content Outline

1. Domain 1: Patient-Centered Pharmacotherapy
    a. Task 2: Disseminate pharmacotherapy plans to patients, caregivers, and interprofessional team members, using appropriate forms of communication and patient education strategies to optimize outcomes: Knowledge of 6
2. Domain 2: Drug Information and Evidence-Based Medicine
    a. Task 3: Conduct pharmacotherapy-related research, using appropriate scientific principles in order to ensure optimal patient care: Knowledge of 3.
3. Domain III: System-Based Standards and Population-Based Pharmacotherapy
    a. Task 1: Implement effective medication use systems in order to improve system- and population-based pharmacotherapy: Knowledge of 1, 2, 4, 6.
    b. Task 2: Incorporate health information technology into patient care processes in order to ensure effective medication use: Knowledge of 1.
    c. Task 3: Employ safety systems in accordance with established standards in order to promote a safe medication use process: Knowledge of 1, 2, 3.
    d. Task 4: Implement public health initiatives that target recognized benchmarks in order to improve population health: Knowledge of 1.

OVERVIEW

The purpose of this review of policy, practice, and regulatory issues is to highlight areas of importance for clinical pharmacists as they pertain to policies governing patient care delivery and clinical research activity. Specifically, this chapter addresses rules, regulations, and quality initiatives at the institutional and national levels.

I. CONGRESSIONAL OVERVIEW, COMMITTEES WITH JURISDICTION OVER HEALTH-RELATED POLICY, AND THE LEGISLATIVE PROCESS

A. Congress is bicameral, with two legislative chambers: the Senate and the House of Representatives.

B. The Senate is composed of 100 elected voting members. Legislation and tasks are divided into 20 standing committees, 68 subcommittees, and 4 joint committees. The committees that have jurisdiction over health-related policy include:
   1. The Appropriations Committee, which writes the legislation that allocates federal funds to the many government agencies, departments, and organizations on an annual basis and, in particular, funds discretionary programs.
   2. The Finance Committee, which has jurisdiction over issues that pertain to taxation and health programs under the Social Security Act, including Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).
   3. The Health, Education, Labor and Pensions (HELP) Committee, as it pertains to health, authorizes agencies, institutes, and programs under the Department of Health and Human Services (DHHS), which includes the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC).
   4. The Committee on Veterans' Affairs, which oversees veteran's issues, including the Veterans Affairs health system.
   5. The Aging Committee, which was initially established as a temporary committee but transitioned to a permanent special committee without legislative authority for matters relating to older Americans.
   6. Legislation is reviewed by the committee with the greatest jurisdiction over the provisions in the bill. For example, the Pharmacy and Medically Underserved Areas Enhancement Act (S. 314), introduced in the Senate in 2015, was referred to the Committee on Finance because it amends the Medicare program.

C. The House of Representatives is composed of 435 elected voting members and six delegates from the U.S. territories or from Washington, D.C., with nonvoting privileges. Legislation and tasks are divided into 20 standing committees, four joint committees, and one select committee. Several committees have jurisdiction over health-related policy:
   1. Appropriations has jurisdiction similar to that listed above.
   2. Ways and Means has jurisdiction over taxation and most programs authorized by the Social Security Act, similar to the Senate Finance Committee.
   3. Energy and Commerce, the oldest standing committee of the House of Representatives, has oversight of DHHS and is similar to the Senate HELP Committee.
   4. Veterans Affairs oversees issues related to veterans' concerns.
   5. Legislation is sent to any committee that has jurisdiction over any of the provisions in the bill. For example, the companion bill to S. 109, the Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592), introduced in the House in 2015, was referred to the Subcommittees on Health in both the Energy and Commerce and Ways and Means committees.

D. Legislative Process (Figure 1)
   1. Legislation is drafted by a member of Congress, a congressional committee, a constituent, a state legislature, or an executive communication from the president or an administrative agency.
   2. Types of legislation:
      a. Bills are introduced into either the House or the Senate (prefixed H.R. or S., respectively) as one of two types:
         i. Authorization bills grant authority for a program or agency to exist or promulgate regulations. Once approved, authorization bills will ultimately need an appropriations bill to be introduced and approved in order to receive funding.
         ii. Appropriation bills designate and commit a sum of money designated for a particular purpose by an act or bill.
         iii. Companion bills, such as the Pharmacy and Medically Underserved Areas Enhancement Act, may be introduced separately or simultaneously into the House and Senate.
      b. Once introduced, the legislation is generally referred to the relevant committees for consideration, markup, and approval.
      c. Action, debate, and voting on legislation, which are dictated by rules, differ greatly between the Senate and the House of Representatives.
      d. Because identical versions of a bill must be approved by the two chambers, conference committees work to draft a compromise bill, acceptable to both chambers, that will go to the president.

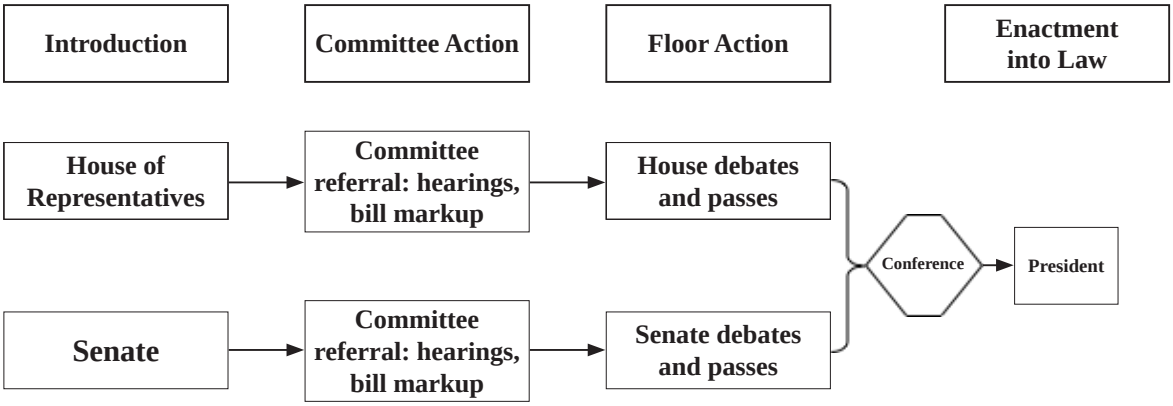

Figure 1. Legislative process.

E. Creation and codification of regulation by the authorized U.S. government department or agency is discussed in the next section.

F. Types of appropriations, or funding:
   1. Mandatory spending, representing government spending on certain programs that are required by law, includes:
      a. Entitlement spending, which authorizes funding to be appropriated for the amount needed to meet the need of those entitled to the benefit for programs such as Medicare, Medicaid, and Social Security; exact levels are automatically set on the basis of the number of eligible recipients, with amounts changed only with eligibility criteria changes
      b. Direct spending, which includes funding required specifically by an authorization bill
   2. Discretionary spending levels are determined annually by Congress; spending is optional. DHHS agencies such as the FDA are funded through discretionary spending.
   3. Continuing resolution continues funding for a program if the congressional fiscal year, ending September 30, ends without a new appropriation in place.

II. U.S. GOVERNMENT DEPARTMENTS AND AGENCIES WITH PRIMARY REGULATORY IMPACT ON THE PRACTICE OF PHARMACY

A. The executive branch comprises the president's cabinet and the heads of 15 executive departments, including DHHS, the Department of Justice (DOJ)—which includes the Office of the Attorney General—and the Department of Veterans Affairs.

B. DHHS is the agency charged with protecting the health of Americans. At 32% of federal monies, appropriations to DHHS represent the largest share of nondefense discretionary funding. The following agencies are part of DHHS:
   1. The FDA is responsible for the safety of most foods (human and animal) and cosmetics, and it regulates both the safety and the effectiveness of human drugs, biologics (e.g., vaccines, blood products, therapeutic proteins), medical devices, and animal drugs.
   2. CMS administers Medicare, Medicaid, and CHIP. It has driven the Value-Based Purchasing (VBP) Program, the Medicare Shared Savings Program (MSSP), and the Electronic Health Record (EHR) Meaningful Use Incentive Program, and it develops Conditions of Participation (CoP) and Conditions for Coverage that health care organizations are required to meet in order to participate in Medicare and Medicaid programs.
   3. The Agency for Healthcare Research and Quality (AHRQ) supports research that helps people make better-informed decisions and improves the quality of health care services. The Public Health Service Act of 1998 authorized AHRQ to convene the U.S. Preventive Services Task Force (USPSTF). The USPSTF is an independent panel of experts on evidenced-based practices for preventive health care who develop clinical recommendations for preventive services.
   4. The CDC provides programs that reduce the health and economic consequences of the leading causes of death and disability. An example is Healthy People, which provides science-based national goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts.
   5. The Health Resources and Services Administration (HRSA) improves access to health care through programs that strengthen the health care workforce, build healthy communities, and achieve health equity for people who are geographically isolated and/or economically or medically vulnerable. HRSA houses the National Center for Health Workforce Analysis, charged with estimating the supply and demand for health care workers and designating shortage criteria in order to establish Health Professional Shortage Areas or Medically Underserved Areas or Populations.

C. DOJ has jurisdiction over the Drug Enforcement Administration (DEA), which prevents, detects, and investigates the diversion of controlled substances and monitored chemicals

D. The U.S. Environmental Protection Agency (EPA) seeks to protect human health and the environment.
   1. Through the Resource Conservation and Recovery Act of 1976, the EPA has jurisdiction over rules governing the disposal of solid and hazardous waste.
   2. The Management Standards for Hazardous Waste Pharmaceuticals Rule proposes new regulations for health care facilities (including pharmacies) and reverse distributors in the handling of hazardous waste pharmaceuticals in order to improve environmental protection.

E. Departments and agencies of the U.S. government make rules and adjudicate (enforce) them within areas of delegated authority.
   1. The Administrative Procedure Act of 1946 granted agencies of DHHS the power to promulgate rules and regulations that have the effect of substantive law.
   2. Proposed codification of general and permanent rules is published in the Federal Register, and the public is allowed to provide feedback during a prespecified period.

3. Final rules are published in the Code of Federal Regulations (CFR), which has 50 titles that are updated every year on a staggered basis.
    a. Title 21: Food and Drugs
        i. Contains rules related to the FDA, DEA, DOJ, and Office of National Drug Control Policy
        ii. Pregnancy and Lactation Labeling Rule (21 FDA CFR Part 201) requires changes to the content and format for drug labeling to assist in the risk-benefit assessment for medication use related to pregnancy and lactation and includes the removal of pregnancy letter categories.
        iii. Institutional Review Boards (21 FDA CFR Part 56) contains standards for the composition, operation, and responsibility of an institutional review board (IRB) that reviews and approves of studies for products regulated by the FDA and regulates human subjects research that involves an investigational drug or device or when an approved product is being used in an investigation. This rule includes clinical investigations designed for submission to the FDA in support of an application or marketing permit. Exemptions from an IRB requirement are outlined in the text of this rule. Differences exist between this regulation and that of the Common Rule (Title 45) for the definitions of research, human subjects, and IRB (discussed later). Both must be considered in the conduct of research.
        iv. Disposal of Controlled Substances (21 CFR DOJ DEA Parts 1300, 1301, 1304, et al.) governs the secure disposal of controlled substances by DEA registrants and ultimate users.
    b. Title 42: Public Health
        i. Contains rules related to HHS, CMS, and the HHS Office of Inspector General (OIG) (which fights fraud, waste, and abuse among DHHS programs)
        ii. Federally qualified health centers, organizations that receive grants for enhanced reimbursement from Medicare and Medicaid for offering health care services to all patients, regardless of their ability to pay, are regulated by rules outlined in Medicare CMS regulations in Title 42.
        iii. Changes in Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements for CMS (42 CFR DHHS CMS parts 424 and 31) expands the definition of non-physician practitioners on hospital staffs to include pharmacists.
    c. Title 45: Public Welfare
        i. Common Rule (45 CFR Part 46): Federal Policy for the Protection of Human Subjects (recently updated in January 2017) protects human subjects involved in research conducted or sponsored by any agency within the DHHS (discussed later). It defines an IRB in the context of the rule and is different from that of 21 CFR 56.
        ii. HIPAA (45 CFR Parts 160, 162, and 164) protects personal health information (PHI).
            (a) It is enforced by the DHHS Office for Civil Rights.
            (b) The suite of HIPAA regulations for patient privacy and security is outlined in the Transactions and Code Set Standards, Identifier Standards, Privacy Rule, Security Rule, Enforcement Rule, and Breach Notification Rule.

III. RECENT LEGISLATIVE ACTIVITY WITH REGULATORY AND HEALTH POLICY IMPLICATIONS

A. The American Recovery and Reinvestment Act (ARRA) of 2009 includes the Health Information Technology for Economic and Clinical Health (HITECH) Act.
    1. HITECH authorizes DHHS to create programs to improve health care quality, safety, and efficiency through the promotion of health information technology, including EHRs and health information exchanges (HIEs) to facilitate and expand the secure electronic movement and use of health information among organizations in accordance with nationally recognized standards.

a. HITECH created the Office of the National Coordinator for Health Information Technology to coordinate nationwide standards and implementation efforts
b. The Standards and Certification Criteria Final Rule is the initial approach to adopting standards, implementing specifications, and providing certification criteria to increase the interoperability, functionality, utility, and security of health information technology and to support its meaningful use.
c. An HIE is defined as a process for exchanging health information through one of three forms:
    i. Directed exchange: Ability to send and receive secure information electronically between care providers to support coordinated care (e.g., allows a primary care provider to send a medical summary to a specialist during a referral)
    ii. Query-based exchange: Ability of providers to find and/or request information on a patient from other providers (e.g., allows emergency department providers to retrieve individual patient records after patient consent)
    iii. Consumer-mediated exchange – Ability of patients to aggregate and control the use of their health information among providers (e.g., online portals that allow patients to track results and update demographic or health information)
d. A health information organization, or HIO, is a model for exchanging information at the local, regional (known as a RHIO [regional health information organization]), or state level.

2. Under ARRA, CMS issued the Electronic Health Records Incentive Programs to provide a financial incentive to health care professionals, hospitals, and Medicare Advantage Organizations that are "meaningful users" of EHRs.
    a. Meaningful use consists of three stages:
        i. Stage 1 targets data capture and sharing (completed in 2014).
        ii. Stage 2 targets advancement in clinical practices (through 2017).
        iii. Stage 3 targets improvement in outcomes (by 2018).
    b. Meaningful users meet several objectives that demonstrate both the use of certified EHRs in a meaningful manner (e.g., e-prescribing) and those that demonstrate the use of certified EHR technology for electronic exchange of health information
        i. Opportunities for pharmacists include the provision of medication reconciliation for at least 50% of patients at transitions of care, as included in the HIE objective.
        ii. Each stage requires more provider-generated prescriptions to be queried against a drug formulary and submitted to pharmacies electronically.
3. HITECH also imposes penalties for breaches of HIPAA and PHI, enforced by the Office for Civil Rights within DHHS.

B. The Patient Protection and Affordable Care Act of 2010 (ACA) contains several provisions, ranging from protecting consumers to improving health care quality and lowering costs to increasing access to care.
1. It mandates that new health plans cover USPSTF recommendations receiving a high rating of grade of A or B at no cost to patients
2. The Medicare Shared Savings Program offers providers and systems the opportunity to participate in accountable care organizations (ACOs). ACOs are a set of providers associated with a defined population of patients accountable for the quality and cost of care delivered to that population. Pharmacists may aid ACOs in achieving these quality goals.
3. The ACA provides opportunities for pharmacists to participate in the Medicare Annual Wellness Visit,
4. The ACA created the CMS Innovation Center to pioneer novel care delivery and payment models in which opportunities for pharmacists may exist:
    a. The Comprehensive Primary Care (CPC) initiative explores whether reimbursable comprehensive primary care can result in better outcomes at reduced costs.

b. The Community-Based Care Transitions Program (CCTP) explores models for reducing readmissions in high-risk patients. It is led by the Partnership for Patients, a nationwide initiative to reduce preventable errors in hospitals and readmissions.
c. The Independence at Home Demonstration Program promotes the interdisciplinary collaboration of clinicians to provide home-based medical care for Medicare beneficiaries and test the effectiveness of delivering comprehensive primary care services at home and determine whether doing so improves care for Medicare beneficiaries with multiple chronic conditions.

5. The ACA also created an optional Medicaid State Plan benefit that allows states to establish Health Homes to provide comprehensive care for Medicaid patients with chronic conditions

C. The Biologics Price Competition and Innovation (BPCI) Act of 2009 is a provision in the ACA that creates an abbreviated approval pathway for follow-on biologic products, known as biosimilars.

D. The Physician Payments Sunshine Act (i.e., Sunshine Act) authorized CMS to require manufacturers of drugs, medical devices, and biologicals that participate in federal health care programs to report payments and items of value given to physicians and teaching hospitals. It also requires manufacturers and group purchasing organizations to report physician ownership or investments as part of the Open Payments Program.

E. The Safe and Secure Drug Disposal Act of 2010
1. This legislation authorized the DEA to promulgate rules for patient and long-term care facility disposal of unused controlled substances.
2. The Disposal of Controlled Substances Final Rule allows the transfer of unwanted and unused controlled substances from an ultimate user (i.e., patient) to an authorized collector for safe, secure, and responsible disposal.
a. Authorized collectors include manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies
b. Allows ultimate users to voluntarily dispose of controlled substances through take-back and mail-back events and in collection receptacles
c. Regulates each element of the disposal process, including transfer, deliver, collection, return, and recall of controlled substances

F. The FDA Safety and Innovation Act of 2012
1. Amends the federal Food, Drug, and Cosmetic (FD&C) Act to reauthorize PDUFA through 2017 and authorized the Generic Drug User Fee Act and the Biosimilar User Fee Act to collect fees for product applications, supplements, and other services
2. Permanently incentivizes pediatric drug studies to enhance accurate labeling
3. Addresses drug shortages and states that the manufacturer of a drug that is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, must notify the Secretary of the DHHS of a permanent discontinuation in the manufacturing of the drug that may disrupt supply in the United States, together with the reasons for discontinuation, at least 6 months before the date of discontinuation
4. Additional provisions include responding to those failing to report a shortage, expediting manufacturer inspections, publishing a drug shortage list, authorizing hospitals to repackage drugs without registering as an establishment if distributing within a health system, and requiring the Comptroller General to conduct a study on the impact of medication shortages.

G. The Drug Quality and Security Act (DQSA) of 2013
   1. Establishes a new section (503B) in the Food, Drug, and Cosmetic Act of 1938 (FD&C Act) to allow a compounding facility to voluntarily register as an outsourcing facility with the FDA (Table 1).
      a. The outsourcing facility must give a licensed pharmacist direct oversight over compounded drugs.
      b. Among other requirements, only drugs with bulk ingredients listed as approved by the secretary may be compounded; also, the facility must report to the secretary every 6 months and undergo inspection by the FDA, report serious adverse events, and label products identifying them as compounded drugs.
   2. Adds a new section (582) to the FD&C Act with product-tracing requirements ("track and trace") for drug manufacturers, repackagers, wholesale distributors, and dispensers to provide transaction details when pharmaceutical products change ownership. Entities must also respond promptly in the event of a recall or suspicion or investigation of an illegitimate product.

Table 1. Basic Comparison of Compounding of Drug Products Under Sections 503A and 503B

Category	503A: Traditional Compounder	503B: Outsourcing Facility
FDC Act exemptions	Good manufacturing practices Specific labeling requirements FDA approval before marketing	Specific labeling requirements FDA approval before marketing
Compounding practice	Compounded for identified individual patient Must follow USP guidance for compounding	Sterile compounding May or may not obtain prescriptions for individual patients Must follow good manufacturing practices for compounding
Reporting and registration	No reporting or registration Must follow track-and-trace requirements	FDA registration voluntary Reports of compounded products and bulk ingredients every 6 months Exemption from track-and-trace requirements
Fees	None	Establishment and inspection fees
Shipping restrictions	Under state regulations	None

FDA = U.S. Food and Drug Administration; USP = United States Pharmacopeia.

H. Medicare Access and CHIP Reauthorization Act (MACRA) of 2015
   1. Repealed the sustainable growth rate (SGR) physician reimbursement methodology that threatened to reduce Medicare physician payments for more than a decade
   2. Represents a shift in reimbursement from fee-for-service to pay-for-performance or pay-for-value:
      a. Establishes an alternative payment model (APM) for physicians participating in patient-centered medical homes (PCMHs), ACOs, and Medicare shared-savings programs
      b. Establishes the merit-based incentive payment system (MIPS) that reimburses on the basis of quality, resource use, clinical practice improvement activities, and meaningful use of EHR
         i. Sunsets three existing value-based payment adjustments: the EHR incentive program ("meaningful use"), the Physician Quality Reporting System, and Value-Based Payment Modifier (discussed later) and combines them into MIPS
         ii. Bases payment rate on provider performance in four categories—quality, advancing care information (includes "meaningful use"), improvement activities (emphasizes PCMH participation), and cost (cost performance category not scored for the 2017 performance period, but clinicians will receive feedback on their cost performance)

c. The first reporting year for providers enrolled in either program is 2017, with payment adjustments beginning in 2019.
d. MACRA also reauthorized CHIP through fiscal year 2017. CHIP funding expired in September 2017 without reauthorization.

I. 21st Century Cures Act
1. The act is aimed at streamlining approvals through several initiatives, including a limited population pathway for anti-infectives, accelerated approval for "regenerative therapy," the use of new designs in FDA approvals (e.g., common control arm for multiple trials to speed recruitment and new statistical models to improve approval time), encouragement of the FDA to review and share pathways for biomarkers and outcome assessment methods that may expedite review, and streamlining of differences between the HHS and FDA human subjects' protection rules and IRBs, approval of combination products, and approval of high-risk medical devices.
2. The Cures Act is also aimed at including the patient voice/experience into approval data and processes while allowing the compassionate use of investigative drugs for outside clinical trials in terminally ill patients.
3. The act encourages innovation through the sharing of data by NIH funding recipients and reduces burden on researchers by excluding NIH researchers from the Paperwork Reduction Act
4. The act addresses workforce provisions, including ensuring that women, children and racial/ethnic minorities are appropriately represented in clinical research and by supporting the NIH's Next Generation Researchers Initiative
5. The act supports high-priority NIH initiatives such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN), Precision Medicine, and Cancer Moonshot initiatives and recommends new initiatives such as antimicrobial resistance monitoring by the CDC
6. The act increases funding for mental health, opioid addiction treatment, and the NIH. This funding is discretionary and requires annual Congressional approval.

J. The FDA Reauthorization Act of 2017 (S. 934, H.R. 2430)
1. These companion bills amend the FD&C Act to revise and extend the user fees for prescription drugs, medical devices, and biosimilar/biologic products through 2022.

K. Introduction of the Pharmacy and Medically Underserved Areas Enhancement Act (S. 109 and H.R. 592)
1. These bills would enable pharmacists to provide reimbursable services to eligible Medicare Part B beneficiaries living in medically underserved communities.
2. The bipartisan bill was a result of the combined efforts of pharmacy organizations and advocates, receiving wide support in the House and Senate, with 206 co-sponsors in the House and 43 co-sponsors in the Senate.
3. The companion bills were introduced in January 2017. S. 109 has since been referred to the Committee on Finance

L. The American Healthcare Act (H.R. 1628) and drafts of the Better Care Reconciliation Act of 2017 and the Obamacare Repeal Reconciliation Act of 2017
1. The American Healthcare Act (AHCA) passed the House in May 2017. This reconciliation bill would repeal and alter the parts of the ACA related to the federal budget, such as individual and employer mandates, taxes, and the Medicaid program.
2. The Senate version, named the Better Care Reconciliation Act (commonly referred to as "repeal and replace") has not been officially introduced in the Senate at the time of this writing. At the time of this writing, the Obamacare Repeal Reconciliation Act (commonly referred to as "repeal and delay") is also being considered and has not been officially introduced in the Senate.

IV. THE U.S. FOOD AND DRUG ADMINISTRATION AND THE PRESCRIPTION DRUG APPROVAL PROCESS

A. The Basics of the FDA and the Prescription Drug Approval Process
   1. Most federal laws that authorize the FDA to promulgate rules are enacted by amendments to the FD&C Act, and they are organized in Title 21 of the CFR.
   2. The FDA is funded through discretionary spending every fall in the appropriations bill written by the Senate and House appropriations committees, but the Senate HELP and the House Energy and Commerce committees have jurisdiction over its reauthorization.
   3. Organized by the Office of the Commissioner, Medical Products and Tobacco, Foods and Veterinary Medicine, and Global Regulatory Operations and Policy. The following offices and centers affect medication use:
      a. The Office of the Commissioner conducts overall agency coordination; the FDA's top official, the commissioner, requires Senate confirmation.
      b. The Office of Regulatory Affairs, the largest office, regulates all inspection and enforcement activities.
      c. The National Center for Toxicological Research supports the six product centers with scientific technology, training, and technical expertise.
      d. The Center for Drug Evaluation and Research (CDER) regulates prescription and nonprescription drugs.
      e. The Center for Biologics Evaluation and Research (CBER) regulates biologic products, including vaccines, blood products, and gene therapy.
      f. The Center for Devices and Radiological Health regulates medical devices.
      g. The Center for Food Safety and Applied Nutrition regulates most foods, food additives, infant formulas, dietary supplements, and cosmetics.
      h. The Center for Tobacco Products regulates tobacco-containing products.
      i. The Center for Veterinary Medicine regulates feed, drugs, and devices used for pets, farm animals, and other animals.
   4. Definitions
      a. A clinical trial is a research study of humans conducted to answer specific questions about vaccines, new therapies, or new ways of using known treatments. Clinical trials are required by the FDA to determine whether new drugs or treatments are both safe and effective.
      b. An Investigational New Drug Application (INDA) is submitted to the FDA's CDER for a new drug, a new indication, or an off-label use that will be used in a clinical investigation's preclinical development for that drug to be distributed across state lines for its preclinical development.
      c. A New Drug Application (NDA) is submitted to the FDA's CDER and is the vehicle by which drug sponsors formally propose that the FDA conduct a full review to approve a new pharmaceutical for sale and marketing in the United States.
      d. The Abbreviated New Drug Application (ANDA) contains data that, when submitted to the FDA's CDER, Office of Generic Drugs, permit the review and ultimate approval of a generic drug product.
      e. An authorized generic drug is a listed drug that is marketed, sold, or distributed directly or indirectly to the retail class of trade. Its labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, and/or trademark differs from that of the listed drug.
      f. A biologics license application is submitted to the FDA's CBER and contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology, and medical effects of a biologic product (monoclonal antibodies, enzymes, immunomodulators, growth factors, and cytokines) for which approval to for marketing in the United States is being sought.
      g. The interchangeability of a biosimilar product may allow it to be substituted for the legend (brand) biologic with an expectation that the same clinical outcome will occur and without the requirement of notification or intervention of a prescriber.

B. History of the Regulation of Drugs and Human Subjects Research
   1. The Drug Importation Act of 1848: Prohibited the importation of unsafe or adulterated drugs at key ports of entry
   2. The Biologics Control Act of 1902
      a. Mandated annual licensing of establishments to manufacture and sell vaccines, sera, antitoxins, and similar products in interstate commerce
      b. Authorized the Hygienic Laboratory, precursor to the NIH, to conduct regular inspections for purity and potency
   3. The Pure Food and Drug Act of 1906
      a. Prohibited interstate commerce of adulterated or misbranded drugs
      b. Required labeling of selected dangerous and addictive substances
      c. Identified the United States Pharmacopeia and the National Formulary (USP/NF) as official standards for drugs
   4. The Food, Drug and Cosmetic Act of 1938
      a. Required that firms prove evidence of safety to the FDA before marketing
      b. Placed drug advertising under the jurisdiction of the Federal Trade Commission
      c. Recognized the USP/NF as the official compendia of drug standards
   5. The Durham-Humphrey Amendment of 1951: Amended the FD&C Act of 1938 to statutorily differentiate prescription and nonprescription drugs
   6. The Kefauver-Harris Amendments of 1962
      a. Established the requirement that drug firms demonstrate efficacy as well as safety
      b. Established a statutory requirement to obtain informed consent for research subjects
      c. Authorized the FDA to regulate advertising of prescription drugs and establish good manufacturing practices
   7. The Comprehensive Drug Abuse Prevention and Control Act of 1970 (i.e., the Controlled Substance Act): Authorized the DEA and FDA to regulate the manufacture, classification (schedule), importation, possession, use, and distribution of controlled substances
   8. The Orphan Drug Act of 1983: Established grants, federal assistance for research, and tax incentives to develop drugs targeted to patient populations of fewer than 200,000 and those with no expectation of cost recovery
      a. Grants a period of market exclusivity to new medications (7 years) for these rare diseases (Box 1)
      b. This timeline is independent of patent life (20 years), which begins when a new molecule is invented, not when it gains approval.

Box 1. Suboxone Orphan Drug Status Timeline

- The first patent for Suboxone was filed in 1990.
- While it was being investigated under an IND, the manufacturer filed for orphan drug status in 1993. The application reflected that, despite the high rates of opioid addiction, fewer than 200,000 patients would be using the medication for opiate detoxification and maintenance. In addition, the application noted that market projections found no reasonable expectation that the costs of developing the drug would be recovered from sales. The drug was granted Orphan Drug Status in 1994.
- Suboxone was FDA approved in 2002, and the market exclusivity of 7 years began.
- Market exclusivity for this product lapsed in 2009. The FDA began accepting applications for generic products. The product patent for this formulation expired in 2010.
- The first generic formulations were brought to market in 2013.
- Controversy continues over the original estimates and approval of the product as an orphan drug.

9. The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act): Authorized the FDA to create an abbreviated regulatory pathway through the ANDA for generic drugs
    a. Grants a period of market exclusivity to new medications (4 or 5 years) or new indications (3 years) from approval until the acceptance of applications for generic drugs
    b. Grants the first approved generic drug 180 days of market exclusivity before other generic drugs may be approved
    c. Timeline independent of patent life
10. The Food and Drug Administration Act of 1988: Officially established the FDA as an agency in the DHHS
11. The Prescription Drug User Fee Act of 1992 (PDUFA)
    a. Requires drug, biologics, and medical device (Medical Device User Fee Amendments) manufacturers to pay fees for product applications, supplements, and other services
    b. Reauthorized every 5 years (1997, 2002, 2007, 2012; 2017)
12. The Dietary Supplement Health and Education Act of 1994: Allows nutritional supplements and vitamins to be regulated
13. The FDA Modernization Act of 1997
    a. Streamlines clinical research on drugs and devices
    b. Carries exclusivity provisions for pediatric drugs
    c. Authorizes the creation of a databank (ClinicalTrials.gov) to provide easy access to information on federally and privately supported clinical trials for a wide range of diseases and conditions
    d. Provides abstracts of clinical study protocols that investigators are required to submit
        i. Summary and purpose of study
        ii. Recruiting status
        iii. Criteria for patient participation
        iv. Location for trial and specific contact information
        v. Research study design
        vi. Phase of trial
        vii. Disease or condition and drug or therapy under study
    e. More than 200,000 clinical trials have been listed, with locations in all 50 states and 191 countries.
    f. Reauthorized PDUFA through 2002
14. The FDA Amendments Act (FDAAA) of 2007
    a. Statutory authority to require Risk Evaluation and Mitigation Strategies (REMS) for the safe use of medications (discussed later)
    b. Expanded the requirements for the types of drugs that must be registered on ClinicalTrials.gov; requires the submission of results for certain clinical trials
    c. Reauthorized the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act: Programs designed to encourage more research into, and more development of, treatments for children
    d. Reauthorized PDUFA through 2012
15. The Family Smoking Prevention and Tobacco Control Act of 2009: Gave the FDA authority to regulate tobacco products
16. The BPCI Act of 2009, passed as a provision within the Patient Protection and Affordable Care Act of 2010 (ACA)
    a. Established a regulatory approval pathway for biosimilars
    b. Created FDA-administered periods of regulatory exclusivity for certain brand-name drugs and follow-on products
    c. Created a patent dispute resolution procedure for use by brand-name biosimilar manufacturers

17. The Reducing Prescription Drug Shortages Executive Order, signed by President Barack Obama on October 31, 2011, requires the FDA to:
    a. Broaden the reporting of manufacturing discontinuances that may lead to shortages of drugs that are life supporting or life sustaining or that prevent debilitating disease
    b. Expedite regulatory reviews (including new drug suppliers, manufacturing sites, and manufacturing changes) to avoid or mitigate existing or potential drug shortages
    c. Communicate to the DOJ any evidence of or behaviors by market participants that have contributed to stockpiling or exorbitant pricing
18. The FDA Safety and Innovation Act of 2012 (reviewed earlier)
    a. Established the Biosimilar User Fee Act of 2012 to assess and collect fees for biosimilar biological products
    b. Established the "breakthrough therapy" drug approval pathway
    c. Increased stakeholder involvement in FDA processes by providing for the establishment of a patient-focused drug development initiative
    d. Reauthorized PDUFA through 2017
19. The DQSA of 2013 (reviewed earlier)

C. New Prescription Drug Approval Path
    1. The 1962 Kefauver-Harris Amendments, including a provision requiring manufacturers of drug products to establish a drug's effectiveness with "substantial evidence"
        a. It had been the FDA's position, on the basis of the language of the statute and the legislative history of the 1962 amendments, that Congress generally intended to require at least two adequate and well-controlled trials, each convincing on its own, to establish effectiveness.
        b. The United States Food and Drug Administration Modernization Act of 1997 stated that the agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if the FDA determines that such data and evidence are sufficient to establish effectiveness.
    2. Preclinical studies
        a. Laboratory and animal studies that assess safety and biologic activity of the IND in various model systems
        b. Toxicologic studies of the fetus in pregnant mice, rats, rabbits, or baboons. These studies may or may not translate to human beings and are the basis for pregnancy categorization
    3. An INDA is drafted and submitted to the FDA. It must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, manufacturing, and control of the drug.
    4. Phase I drug trial
        a. The initial introduction of an IND into humans typically involves 20–80 healthy volunteers after INDA approval.
        b. The goal is to garner information on the pharmacokinetic and pharmacodynamic properties and safety profile of the investigational drug to design a well-controlled and robust phase II trial.
    5. Phase II drug trial
        a. Controlled clinical studies are conducted in no more than several hundred subjects
        b. The goal is to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under investigation and to determine the common short-term adverse effects and risks associated with the drug.

6. Phase III drug trial
    a. The investigational drug is administered to a range of several hundred to several thousand patient subjects in different clinical settings to confirm its safety, efficacy, and appropriate dosage.
    b. The goals are to gather necessary additional information about effectiveness and safety for evaluation of the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
    c. This is the step before the sponsor's submission of an NDA to the FDA for approval to market the drug (Box 2).
7. An NDA is submitted to the FDA and classified with a code that reflects both the type of drug being submitted and its intended uses. Not all phase III drugs are approved, and the FDA may impose a clinical hold at any stage.
8. Phase IV drug trial
    a. Also called postmarketing studies
    b. Verify effectiveness or focus treatment on special populations
    c. May be required by the FDA to identify additional information about the drug's risks, benefits, and optimal use

Box 2. Components of a New Drug Application

Index	Safety update report
Labeling information	Statistical analysis
Summary	Case report tabulations
Chemistry, manufacturing, and control	Case report forms
Nonclinical pharmacology and toxicology	Patient information & certification
Human pharmacokinetics and bioavailability	User fee cover sheet
Clinical microbiology (for antimicrobial drugs only)	Financial disclosure
Clinical data	Other pertinent information

D. Generic Drug Approval
1. A generic drug product is identical to an innovator drug product in bioequivalence and pharmaceutical equivalence as required by the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act). Demonstrations of bioequivalence indicate that there are no significant differences in the bioavailability (e.g., rate and extent of absorption of the active ingredient) under experimental conditions, such as that shown in vivo or in vitro studies.
    a. Pharmaceutical equivalents share the same active ingredient, dosage form and strength, route of administration, quality, and intended use (Box 3).

Box 3. Standards for Medications to Be Deemed Pharmaceutical Equivalents

Three criteria • Must contain the same active ingredient • Must be the same dosage form and route of administration • Must be of identical strength or concentration, quality, and purity
Differences allowed • Shape • Releasing mechanism • Labeling (limited differences) • Scoring • Excipients (colors, flavors, preservatives)

b. Therapeutic equivalence of generic drugs
    i. All approved multisource products are listed in the FDA's *Approved Drug* Products *with Therapeutic Equivalence Evaluations* (Orange Book). The therapeutic equivalence coding system (A or B rating), helps health care providers determine whether the FDA found a product to be therapeutically equivalent to other pharmaceutically equivalent products. Codes are assigned in accordance with data submitted in an ANDA to demonstrate bioequivalence.
        (a) A code: An approved generic product considered therapeutically equivalent to other pharmaceutical equivalents
        (b) B code: An approved generic product that is not considered therapeutically equivalent to other pharmaceutical equivalents
    ii. Therapeutic equivalents (rated A) may be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.
        (a) Criteria
            (1) Pharmaceutical equivalent
            (2) Demonstrates bioequivalence
        (b) Designates a brand-name drug or a generic drug as the reference-listed drug

2. An ANDA for a generic product must be submitted to CDER's Office of Generic Drugs.
    a. ANDAs generally do not require preclinical or clinical data; rather, they must demonstrate pharmaceutical equivalence and bioequivalence.
    b. Once an ANDA is submitted and approved, the applicant may manufacture and market the generic drug as a safe, effective, and low-cost option to the public.
3. An authorized generic is a drug that is produced by the brand company under the NDA but marketed as a generic. It is identical to the brand alternative in both active and inactive ingredients. The federal FD&C Act establishes a 180-day exclusivity period after approval of an ANDA. During this period, the FDA may not approve other ANDAs for the same drug product. After 180 days, other generic manufacturers may submit ANDAs
4. In an at-risk launch of a generic, a generic drug manufacturer challenges the validity of the existing patent of a brand drug.

E. Biosimilars and Interchangeable Biologic Products
    1. A biologic product is a drug or vaccine that has been produced in living cells.
    2. The ACA amends the Public Health Service Act through part of the legislation known as the BPCI Act. This legislation created an abbreviated licensure pathway for biological products found to be biosimilar or interchangeable with an FDA-approved reference biological product after 12 years of patent exclusivity.
        a. A biosimilar product is a biological product that is highly similar in safety and efficacy to an FDA-approved reference biological product, with only minor differences in clinically inactive components.
        b. An interchangeable biological product is biosimilar to an FDA-approved reference biological product and meets additional standards. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product. Because this interchange is also subject to state regulation, the statewide policy may override federal policy if it is more restrictive.
            i. The Biosimilar Implementation Committee, staffed by CDER, CBER, the Office of Chief Counsel, and the Office of the Commissioner, has developed several guidances for industry that describe the current thinking relating to quality and scientific considerations in demonstrating biosimilarity, clinical pharmacology data required to demonstrate biosimilarity, reference product exclusivity for biological products, and nonproprietary naming of biological products. These guidances do not establish legally enforceable responsibilities of the FDA.

ii. As of this writing, comments on draft guidance for industry closed in March 2017 and final naming guidance and draft interchangeability guidances are awaited.

c. Table 2 compares the regulatory pathway differences between traditional small molecules and biologics for FDA approval.

Table 2. Regulatory Approval Pathway Comparison for Small Molecule and Biologic Products

Product	Regulatory Pathway	Nonproprietary Name	Indications	Interchangeability	Clinical and Trial Data Requirement
Small Molecule (FD&C Act)	New drug application [505(b)1 and 2]	N/A; legend (brand) drug	N/A; legend (brand) drug	N/A; legend (brand) drug	Clinical data required; safety and efficacy data requirement
Generic small molecule	Abbreviated new drug application [505(j)]	Same as originator	Same as originator	Granted with initial approval (e.g., Orange Book rating)	Clinical data not required; bioequivalence data requirement
Biologic (BPCI Act)	Biologics license application [351(a)]	N/A; innovator (reference) drug	N/A; legend (brand) drug	N/A; legend (brand) drug	Clinical data required; purity, safety, and potency data requirement
Biosimilar	Biosimilar application [351(k)]	Uncertain; may be different	May or may not have all indications; extrapolation allowed	Not automatically granted at initial approval; requires additional review (e.g., Purple Book rating)	Clinical data required; abbreviated data requirement with purity, safety, and potency (i.e., totality of evidence)

N/A = not applicable.

F. Medical Devices

1. An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is:
   a. Recognized in the official NF, or the USP, or any supplement to them
   b. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals
   c. Intended to affect the structure or any function of the body of humans or other animals, does not achieve any of its primary intended purposes through chemical action within or on the body, and does not depend on being metabolized for the achievement of its intended purposes
2. Regulated by the Center for Devices and Radiological Health
   a. Categorized by the risks associated with the device into classes I–III. Class III devices, which carry the highest risk, are subject to the greatest regulatory control and must be approved by the FDA before marketing. A manufacturer of a class III medical device must submit a premarket approval application assuring the FDA of its safety and efficacy.
   b. If a medical device is essentially equivalent to an existing, legally marketed device, an investigational device exemption may be filed to allow for clinical study of its safety and effectiveness before a 510(k) is submitted for premarket notification.

G. Risk Evaluation and Mitigation Strategies (REMS)

1. The FDAAA of 2007 authorized the FDA to require REMS to ensure benefits outweigh risks before or after drug approval, if necessary. Examples of drug risks and possible actions include patient education on signs and symptoms; monitoring of laboratory values to help prevent serious adverse effects; the requirement of a negative pregnancy test before medications linked to serious birth defects are dispensed; and administration by a health care professional in the presence of high administration-related risk.

2. Is separate from the FDA's Risk Minimization Action Plans, which is a voluntary program for industry for drugs that carry unusual risks but also unusual benefits
3. Requires that a drug be prescribed and dispensed with one of the following:
    a. Medication guide or patient package inserts
        i. Medication guides are not usually required as part of a REMS.
        ii. If the medication guide is listed as an Element To Assure Safe Use (ETASU), it must be provided in all settings (inpatient and outpatient).
    b. Communication plan to health care providers (for NDAs or biologics license applications only, not ANDAs)
    c. Elements to Assure Safe Use (ETASU) (Box 4)

Box 4. Risk Evaluation and Mitigation Strategies' Requirements of ETASU

ETASU may include one or more of the following:
- Health care providers who prescribe the drug have particular training or experience or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- Drug is dispensed only in certain health care settings
- Drug is dispensed to patients with evidence of safe use conditions, such as laboratory test results
- Each patient using the drug is subject to monitoring
- Each patient using the drug is enrolled in a registry

ETASU = Elements To Assure Safe Use.

4. The FDA does not have the authority to impose penalties on pharmacies and pharmacists not in compliance with REMS requirements, but there may be legal implications, such as misbranding violations or civil liability issues.

Box 5. Suboxone REMS Program

REMS elements include:
- Medication guide
- ETASU
    - Documentation of several safe use conditions by the prescriber:
        - ✓ Patient meets diagnostic criteria
        - ✓ Risks have been explained
        - ✓ Safe storage has been reviewed
        - ✓ Limited quantity prescribed at first visit
    - REMS Instruction Letter to Prescribers mailed annually to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 and all retail pharmacies authorized by the DEA to handle Schedule 3 controlled substances by manufacturer
    - Documented patient monitoring:
        - ✓ Regular visits
        - ✓ Adherence assessments
        - ✓ Appropriate prescribing
        - ✓ Psychosocial support assessment
        - ✓ Progress toward treatment goals

DEA = Drug Enforcement Administration.

5. Critical Path Initiative
    a. Created in response to a significant decline in NDAs, biologics license applications, and medical device applications because of the widening gap between basic science discovery and the challenging, inefficient, and costly development of medical products
    b. Prioritizes the most pressing developmental problems and identifies areas that provide the greatest opportunities for rapid improvement and public health benefit through three dimensions: safety assessment, evaluation of medical utility, and product industrialization
6. The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership that includes government agencies, industry representatives, patient advocacy groups, professional societies, investigator groups, academic institutions, and other stakeholders. It is aimed at improving the quality and efficiency of clinical trials.

V. ACCREDITING ORGANIZATIONS AND QUALITY IMPROVEMENT EFFORTS

A. Accreditation: The Joint Commission
    1. Independent not-for-profit organization that sets standards for the accreditation of health care facilities through its mission "to continuously improve health care for the public, in collaboration with other stakeholders, by evaluating health care organizations and inspiring them to excel in providing safe and effective care of the highest quality and value"
    2. Accredits and certifies almost 21,000 health care organizations in the United States. Accreditation is reassessed every 3 years on the basis of adherence to hospital standards, as assessed during on-site surveys, and quality reporting of performance indicators.
        a. Standards address performance in functional areas of patient rights, patient treatment, medication safety, and infection control. National Patient Safety Goals were established to help accredited organizations address specific areas of concern in patient safety. Goals differ by health care setting and can change on the basis of recommendations from the Patient Safety Advisory Group.
        b. In on-site surveys, which are unannounced, tracer methodology is used to evaluate a patient's medical record as a road map through a health care organization to evaluate its compliance with standards and systems to provide care and services. First-generation tracers follow a patient through care areas, whereas second-generation tracers focus on major organizational areas, such as high-alert medications and medication shortages.
        c. Performance measurement: ORYX is a Joint Commission initiative to integrate outcomes with accountability in core measures (acute myocardial infarction, pneumonia, surgical care improvement project, children's asthma care, perinatal, hospital outpatient measures, venous thromboembolism, substance abuse, tobacco treatment, emergency department care, immunization, hospital-based inpatient psychiatric services, and stroke) in its accreditation process.
            i. Included accountability measures and processes are those that result in the greatest improvement in patient outcomes as identified by the Joint Commission. These measures and processes must be of sound scientific evidence, be in proximity between process and outcome, accurately measure the process, and minimize adverse effects without inducing unintended consequences. Measures are updated semiannually.
            ii. National Hospital Quality Measures include common standardized measures between The Joint Commission and CMS, designed to share a single set of documentation (Box 6).

Box 6. National Hospital Inpatient Quality Measure for Substance Abuse (SUB)-3

Measure: Alcohol and Other Drug Use Disorder Treatment Provided or Offered at Discharge
Type of Measure: Process
Description: Patients who are identified with alcohol or drug use disorder who receive or refuse at discharge a prescription for FDA-approved medications for alcohol or drug use disorder OR who receive or refuse a referral for addictions treatment out of hospitalized inpatients 18 years and older identified with an alcohol or drug use disorder
Rationale: Excessive alcohol and substance abuse negatively affects health and society. Brief interventions have been found improve health and reduce costs

iii. National Quality Measures contain measures not common to CMS.
iv. The Targeted Solutions Tool, created by the Joint Commission Center for Transforming Healthcare, provides a process for accredited hospitals to measure performance, identify barriers to excellent performance, and implement proven solutions.

B. Accreditation and Certification: The National Committee for Quality Assurance (NCQA)
   1. Private, not-for-profit organization with a mission to improve the quality of health care through measurement, transparency, and accountability
   2. Responsible for the development and maintenance of the Healthcare Effectiveness Data and Information Set (HEDIS)
      a. Consists of more than 83 measures across five domains of care that health plans use to measure performance and focus improvement efforts. Domains include effectiveness of care, access of care, experience of care, utilization and relative resource use, and health plan descriptive information.
      b. Several measures are included in CMS's Quality Rating System for health plans participating in federally facilitated marketplaces for consumers to view in 2016.
   3. Voluntary accreditation programs, certification programs, physician recognition programs, and distinctions are directed at health plans (e.g., health maintenance organizations, preferred provider organizations, and consumer-directed health plans), physician networks, medical groups, and individual physicians.
      a. Notably accredits ACOs and certifies and recognizes patient-centered medical homes (PCMHs)
      b. Assessments may include on-site clinical and administrative processes, through data collection for the HEDIS, and measuring member satisfaction through the Consumer Assessment of Healthcare Providers and Systems survey.
   4. The Quality Compass: A comparison tool that allows users to view measure results and benchmark information. The tool ranks health plans using the HEDIS measures
   5. Public reporting: "The State of Health Care Quality," which is an annual, overall assessment of the performance of the American health care system; "America's Best Health Plans" in collaboration with *U.S. News & World Report;* and the online Health Plan Report Card with a searchable database detailing health plans' accreditation and performance ratings

C. The Center for Pharmacy Practice Accreditation: Established by the American Pharmacists Association, the National Association of Boards of Pharmacy, and American Society of Health-System Pharmacists (ASHP), it offers accreditation for pharmacy practice sites on the basis of adherence to comprehensive and patient-centered medication use performance measures. Accreditation includes community, specialty, and telehealth pharmacy practice programs.

D. Quality Improvement Efforts
   1. Development of the National Quality Strategy (NQS)
      a. The Clinton administration formed the President's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry, which recommended steps to provide a "national commitment to improving healthcare quality." This led to the formation of the NQF in 1999 (described below).
      b. Medicare Improvements for Patients and Providers Act of 2008: The DHHS entered into a contract with the NQF to establish a portfolio of quality and efficiency measures for use in reporting on and improving health care quality for the federal government to determine a return on investment in health care spending. This work, in combination with the Institute for Healthcare Improvement's Triple Aim and the Institute of Medicine's 6 Aims, laid the foundation for the development of a NQS.
      c. The ACA officially charged DHHS with developing a NQS. The NQF led the development of the National Priorities Partnership of 52 partner organizations to develop the NQS. The NQS, published in 2011, includes three aims and six priorities for the quality improvement of health care.
   2. Strategies to enhance health care quality
      a. Value-based purchasing: rewarding of high-quality care by such groups as CMS, employer purchasers, health plans and consumers; achieved by measuring and reporting on quality measures
      b. Outcomes-based performance: payment and reimbursement based on the achievement of a specific outcome rather than a single action or service
      c. Publicly reporting data: to drive systems to benchmark and achieve quality care
   3. The National Quality Forum (NQF)
      a. Nonprofit organization comprising stakeholders from consumer organizations, public and private purchasers, physicians, nurses, accrediting and certifying bodies, supporting industries, and health care research and quality improvement organizations.
      b. Aimed at improving quality through a three-part mission:
         i. Building consensus on national priorities and goals for performance improvement and working in partnership to achieve them.
            (a) As a result of the Medicare Improvements for Patients and Providers Act, the NQF identified priorities for health care performance measurement based on evidence related to 20 high-priority conditions.
            (b) The conditions were identified by CMS to account for more than 95% of their costs.
         ii. Endorsing national consensus standards for measuring and publicly reporting on performance; assessing evidence to support and endorse quality measures proposed by other organizations (NCQA, American Medical Association, etc.) through a transparent, consensus-based practice
         iii. Promoting the attainment of national goals through education and outreach programs
   4. The Agency for Healthcare Research and Quality (AHRQ)
      a. The AHRQ is a DHHS agency that supports research to help people make informed decisions and improves the quality of health care services through its mission to improve the quality, safety, and effectiveness of health care for all Americans
      b. Health service research provides clinical, health care system, and public policy decision-makers evidence-based information on health outcomes, quality, cost, use, and access to improve the quality of health care services.
      c. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) supports and promote the assessment of consumer experiences with health care. The surveys assess the patient experience with health care services at multiple levels of delivery (e.g., health plans, hospitals [the Hospital Consumer Assessment of Healthcare Providers and Systems; HCAHPS] and dialysis centers). The CAHPS is used in a variety of assessments, including those by the NCQA.

   d. Hosts the National Quality Measures Clearinghouse, which details summaries of evidence-based quality measures and measure sets used in a variety of settings, endorsed by various organizations, and used in several initiatives, including CMS initiatives
   e. Funding opportunities, toolkits, and resources are available for researchers, clinicians, policy-makers, and consumers.
5. The Patient-Centered Outcomes Research Institute (PCORI): Nonprofit authorized by Congress in 2010 that is charged with improving the quality and relevance of evidence available to help patients, caregivers, clinicians, employers, insurers, and policy-makers make informed health decisions through the support and funding of comparative clinical effectiveness research (CER)
6. The Pharmacy Quality Alliance (PQA)
   a. The mission of the PQA is to improve the quality of medication use across health care settings
   b. Develops medication-related performance measures—including proportion of days covered, gap in medication therapy, diabetes medication dosing, suboptimal treatment of hypertension in patients with diabetes, use of high-risk medications in older adults, drug-drug interactions, and medication therapy for people with asthma—through a collaborative process with key stakeholders
7. CMS Initiatives
   a. Hospital Value-Based Purchasing Program was established by the ACA in 2010 and uses quality measures endorsed by the NQF as well as the AHRQ's HCAHPS to establish and apply criteria for reimbursement and incentive payments. Performance data are public on the Hospital Compare website.
   b. Physician Quality Reporting System ties quality measures to physician reimbursement and makes some data public on the Physician Compare website. Under MACRA, this will be combined into the MIPS program.
   c. Health Insurance Marketplace Quality Rating System (QRS) aims to:
      i. Provide useful information to consumers using the Health Insurance Marketplace. Plans will be required to display their QRS star ratings (5-star scale) on their website before the 2018 Open Enrollment Period (limited pilot for 2017), and ratings will be displayed through the federally facilitated marketplaces. These ratings incorporate quality measures such as the NCQA's HEDIS and several PQA measures.
      ii. Provide actionable information that plans can use for performance improvement
         (a) Quality Bonus Payment Demonstration Project was designed to drive quality improvement by extending bonus payments for improvements to low-performing plans.
         (b) EQuIPP is a performance information management system that makes performance data available to both health plans and pharmacy organizations. Potential opportunity for community pharmacy to improve plan ratings.
      iii. Facilitate oversight of qualified plans
8. The Leapfrog Group is a voluntary program that works with employers to enable and direct purchasing power toward health care decisions focused on safety, quality, and value. It compares hospital performance on the metrics most important to consumers and purchasers of care. A Hospital Safety Grade of A, B, C, D, or F has been applied to more than 2500 hospitals on the basis of prevention of errors, accidents, injuries, and infections.

VI. INSTITUTIONAL MEDICATION USE POLICY CONSIDERATIONS

A. Formulary Management
   1. Basics
      a. Formulary management is an ongoing process by which a health care organization establishes medication use policies on drugs, therapies, and drug-related products that are evidence based and cost effective in certain patient populations.
      b. The Joint Commission Medication Management Standards chapter requires the hospital to develop and approve criteria for selecting medications that include indications for use, effectiveness, drug interactions, potential for errors and abuse, adverse drug events, sentinel event advisories, populations served, other risks, and costs.
      c. The CMS CoP require that medical staff establish a formulary system.
      d. A pharmacy and therapeutics (P&T) committee develops consensus on medication use policies and formulary management.
      e. Evidence-based evaluation of medications for inclusion on a formulary includes a drug use review or drug use evaluation (DUE) and will be affected by CER.
   2. Definitions
      a. Formulary – A continually updated list of medications and related information, developed with the clinical judgment of pharmacists, physicians, and other experts in the diagnosis and treatment of disease and promotion of health within hospitals, health plans, and health care systems
      b. DUE – Process used to assess the appropriateness of drug therapy in which data on drug use in a given health care environment are compared with predetermined criteria and standards
      c. Medication use evaluation (MUE) – Performance improvement method that focuses on evaluating and improving medication-use processes related to prescribing, medication preparation, dispensing, administering, and monitoring. Medication use evaluations are often also tied to cost savings.
   3. Formulary management strategies
      a. Preferential use of generic drugs
      b. Formulary exclusion: Process of limiting medications from the formulary (called non-formulary or non-preferred medications)
         i. Open formulary: Non-formulary or non-preferred medications may be covered at variable levels of cost within a health plan.
         ii. Closed formulary: Non-formulary or non-preferred medications are not covered within a health plan unless under an exception where medically appropriate.
         iii. Formulary restrictions: Restricting prescriptive authority to a particular service or disease state (Box 7)

Box 7. Example Suboxone (Buprenorphine/Naloxone) Sublingual Film Formulary Criteria for Use

Health systems may wish to restrict the use of agents that are deemed high risk, high cost, or as needing special monitoring (e.g., Suboxone)
Criteria for use may include: • Patient inclusion: Patients meeting diagnostic criteria for opioid dependence/use disorder needing opioid agonist therapy • Provider inclusion: Authorized to prescribe Suboxone by meeting all requirements for a waiver specified by the Drug Addiction Treatment Act (DATA) 2000 as codified at 21 U.S.C. 823(g), who has experience in addiction management; assurance of the availability of necessary treatment resources must be completed by the physician before prescribing • Considerations for use: ◦ Alternative first-line therapies for opioid dependence include methadone, though this agent is not available for office-based opioid treatment ◦ Consider the potential for corrected QT interval prolongation in unstable cardiac disease or low potassium concentrations ◦ Consider the potential for drug interactions with CYP3A4 inhibitors or inducers and with central nervous system depressants ◦ Patients will need monitoring for several hours after administration of induction doses ◦ Patients should be seen weekly for the first 2 weeks of therapy and then at least monthly for the next 3 months ◦ Therapy should be discontinued if the patient is found to misuse, abuse, or divert the medication; to be noncompliant with therapy; or to be unresponsive to therapy • System responsibilities: ◦ Procedures to verify provider authorization and to restrict use to authorized prescribers must be in place ◦ Quantity limits may be imposed such that enough medication is dispensed to last only until the next scheduled appointment

CYP3A4 = cytochrome P450 3A4 isozyme.

iv. Therapeutic interchange: Authorized exchange of therapeutic alternatives through written guidelines, policies, or protocols within a formulary system

v. Guided-use requirements: Include use criteria, clinical practice guidelines, and operating procedures

vi. MUE: MUEs differ from DUEs in that MUEs emphasize improving patient outcomes using a process that identifies, resolves, and prevents medication-related problems (actual or potential). Steps in conducting MUEs include:

(a) Establishing and implementing criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies

(b) Selecting medications for MUE on the basis of adverse medication events or risk of events, signs of treatment failures, expense of medication, patient population or disease state

(c) Identifying data points and collecting data

(d) Evaluating adherence to criteria, guidelines, treatment protocols, and standards of care for medications and medication use policies

(e) Interpreting and reporting MUE findings

(f) Identifying and implementing improvement strategies in the medication-use process

2. Medication Safety Monitoring and Reporting

a. Differentiation between medication errors, adverse events, and adverse reactions is critical to the evaluation and risk minimization process. Table 3 outlines the differences between medication errors, adverse drug events, and adverse drug reactions, or non-preventable adverse drug events.

Table 3. Differences between Medication Errors, Adverse Drug Events, and Adverse Drug Reactions

Term	Definition	Example
Medication error	Any error occurring in the medication process (ordering, transcribing, dispensing, administering, and monitoring)	Order filled for the wrong patient
Adverse drug event	Injury resulting from medication use or misuse; may or may not result from a medication error	Hemorrhage from heparin
Preventable adverse drug event	Injury caused by medication error	Overdosage of a medication that resulted in a hospitalization
Potential adverse drug event	Medication error with the potential for injury	Overdosage of a medication that was intercepted before patient administration
Adverse drug reaction	Non-preventable injury caused by the drug at normal doses and with normal use; not a result of a medication error	Allergic reaction in a person with no known allergies

3. Medication errors
    a. In 1999, the IOM released a report titled "To Err Is Human," which stated that medical errors claim as many as 98,000 lives a year. The 2004 IOM report "Patient Safety: Achieving a New Standard for Care" revealed the high incidence of adverse events occurring in hospitals.
    b. The Patient Safety and Quality Improvement Act of 2005 (Patient Safety Act [PSA]) and the Patient Safety and Quality Improvement Final Rule (Patient Safety Rule) were a congressional response to these reports. The Patient Safety Rule requires the AHRQ to administer a Network of Patient Safety Databases to assess national de-identified patient safety events.
        i. Encourages health care providers and organizations to voluntarily report and share patient safety information without fear of legal action
        ii. Authorized the creation of patient safety organizations (PSOs)
            (a) Private or public entities, profit or not-for-profit entities, provider entities such as a health system, or other entities.
            (b) PSOs provide a secure mechanism for the collection, aggregation, and analysis of data to identify and reduce risks and hazards that may occur with patient care delivery.
                (1) The AHRQ created the Patient Safety Organization Privacy Protection Center to support the implementation of the Patient Safety Act. The Privacy Protection Center provides technical assistance to PSOs to ensure that data on patient safety events submitted to the Network of Patient Safety Databases are non-identifiable. PSOs not listed with AHRQ are not recognized under the PSA.
                    (A) Data are submitted to PSOs through Common Formats, developed by AHRQ for acute care hospitals and skilled nursing facilities. Common Formats provide a systematic process for reporting adverse events, near misses, and unsafe conditions, and they allow a hospital to report harm from all causes.
                    (B) The NQF leads the public review and lends expert opinion regarding the Common Formats.
                    (C) In March 2013, CMS communicated that although the use of Common Formats is not required for CoP for Quality Assessment and Performance Improvement surveys, hospitals that use them will be in a better position to meet Quality Assessment and Performance Improvement requirements.
                    (D) CMS surveyors were also encouraged to become familiar with Common Formats.

iii. The ACA charges PSOs to assist health systems with a high rate of risk-adjusted readmission rates to decrease readmission rates and improve transitions of care.
(a) The Institute for Safe Medication Practices was begun in 1975 to promote medication error prevention and initiated a voluntary practitioner error-reporting program. The institute is now a nonprofit PSO that publishes four medication safety alert newsletters for acute care settings, ambulatory care settings, nurses, and medications.
(b) Vizient, formerly known as the University HealthSystem Consortium (UHC), is an alliance of academic medical centers and affiliated hospitals that is listed as an AHRQ-listed PSO under the UHC Performance Improvement PSO. It offers the UHC Patient Safety Net, a web-based inpatient and outpatient safety event–reporting system that consolidates and aggregates data for specific event types and offers best practices and policies to address common systemic areas for improvement

4. Adverse events
   a. Grades of certainty criteria, including certainty/definite, probable/likely, possible, and unlikely/doubtful, determine whether an adverse event is caused by a medication and can be assessed using tools such as the Naranjo Adverse Drug Reaction (ADR) Scale or the World Health Organization (WHO)–Uppsala Monitoring Centre (UMC) Causality Assessment.
   b. Adverse drug events should be reported to the FDA Adverse Event Reporting System (FAERS), a database with more than 400 million adverse event and medication error reports.
      i. MedWatch Form FDA 3500 is for voluntary reporting of a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement by health care professionals. The HIPAA Privacy Rule specifically permits health care professionals to disclose PHI for public health purposes.
      ii. MedWatch Form FDA 3500A is for regulated industry following investigational new drug (IND) and biologic regulations and user facilities such as hospitals and nursing homes.
      iii. MedWatch Form FDA 3500B is available for consumer reporting.
      iv. Submitted events are evaluated by CDER and monitored by CBER.
      v. Vaccine-related adverse effects, veterinary medicine product adverse events, and suspected unlawful internet sales of medical products should not be reported to MedWatch.
         (a) The Vaccine Adverse Event Reporting System is a national postmarketing vaccine safety surveillance program managed by the CDC and the FDA for vaccine-related adverse events to be reported, analyzed, and made available to the public. The National Childhood Vaccine Injury Act of 1986 requires health care professionals and vaccine manufacturers to report to DHHS specific adverse events that occur after the administration of routinely recommended vaccines.
         (b) The FDA's Sentinel Initiative was implemented as a result of the FDAAA of 2007 to proactively monitor the safety of FDA-regulated products such as drugs, vaccines, and medical devices. It is being implemented in stages to complement existing reporting systems, and it will have functionality to query electronic medical records, administrative and insurance claims, and registries.
5. Workplace safety: Occupational Safety and Health Administration
   a. Ensures safe and healthful working conditions for employees
   b. Is part of the U.S. Department of Labor
   c. Was granted regulatory authority through the Occupational Safety and Health Act of 1970
6. Safety of compounded products
   a. The USP develops standards, enforceable by the FDA, for the identity, strength, quality, and purity of medications and dietary supplements, including compounded products.
   b. Pharmacies may be subject to inspection against these standards by boards of pharmacy, the FDA, The Joint Commission, and other entities.

c. The USP General Chapters are as follows: Required (numbered below <1000>), Informational (numbered <1XXX), and Specific for dietary supplements (numbered <2XXX>); the chapters pertaining to compounding include the following:
   i. USP 795: Pharmaceutical Compounding for Nonsterile Preparations
   ii. USP 797 (being revised): Pharmaceutical Compounding for Sterile Preparations (CSPs)
      (a) USP 797 standards historically assign risk levels (low, medium, and high) according to requirements for the types of admixtures and preparation procedures. Proposed revisions limit the risk categories to category 1 and category 2, depending on a product's beyond-use dating. Proposed revisions also introduce "in-use time," before which an ingredient used in a CSP must be used after it has been opened or punctured, or before which a CSP must be used after it has been opened or punctured.
      (b) As a result of deaths associated with microorganism contamination, CSPs have been under scrutiny. In October 2015, CMS issued a revision to its Pharmaceutical Services CoP State Operations Manual aligning its standards of practice for drug compounding with USP requirements, particularly for CSPs.
      (c) An area of interest for organizations is beyond-use dating and sterility for CSPs. According to USP 797, if sterility testing has been performed, pharmacies can assign a beyond-use date based on the maximum chemical stability as listed in valid references. If sterility testing has not been performed, pharmacies must use beyond-use dating in accordance with the level of risk and storage.
      (d) In-use dating: Once opened/punctured, must be used
   iii. USP 800: Hazardous Drugs: Handling in Healthcare Settings

7. Supporting Patient Access to Medications
   a. Options exist for supporting and supplementing patient access to medications. Pharmacists are a conduit for linking patients to medication discount and prescription assistance programs.
   b. The 340B Drug Pricing Program, authorized through the Medicaid Drug Rebate Program in 1990 and expanded by the ACA in 2010, allows specific categories of safety-net providers to become established entities and procure outpatient prescription drugs at discounted prices. The 16 categories of covered entities use the discounts to expand or develop new services.
      i. Eligibility is defined at the level of the health care facility and not the individual; however, the HRSA's Office of Pharmacy Affairs states that only patients with an established relationship with the covered entity are eligible to receive 340B purchased drugs.
      ii. Covered entities can procure drugs at 340B prices and distribute them in the following ways:
         (a) Through in-house pharmacies or to an outpatient clinic for direct administration to patients
         (b) Distribution to the patient from a contracted pharmacy
      iii. In August 2015, the HRSA released a draft "mega guidance" for comment that would have had significant implications for 340B entities, including narrowing the definition of covered patients, prohibiting duplicate discounts for Medicaid Managed Care patients, and increasing pharmacy oversight. The current administration withdrew the guidance, and any further guidance would have to be submitted to the Office of Management and Budget.
   c. Patient and prescription assistance programs are operated by drug manufacturers to provide free medications to patients who cannot afford them.

VII. INSTITUTIONAL REVIEW BOARD IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

A. History
   1. The National Research Act of 1974 created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, partly in response to the Tuskegee Syphilis Study. This group issued the 1978 Belmont Report, summarizing the ethical principles and guidelines for conducting human subjects research.
   2. As a result of the Belmont Report, the Federal Policy for the Protection of Human Subjects (Common Rule) was published in 1991.

B. By federal regulation, every institution that conducts or supports biomedical or behavioral research involving human subjects must have an IRB that initially approves and periodically reviews research protocols to protect the rights of human participants.
   1. A human subject is a living person about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information.
   2. Governed by both FDA Title 21 Part 56 and DHHS Office for Human Research Protections regulations at Title 45 CFR Part 46; requires the IRB or ethics committee to protect the rights, safety, and well-being of all study subjects. Specifically, Title 45 constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects. In 2015, DHHS and 15 other federal agencies announced proposed changes to the Common Rule intended to better protect human subjects involved in research while facilitating valuable research and reducing burden, delay, and ambiguity for investigators. The Final Rule was published in January of 2017 and went into effect January 2018.
      a. Clinical investigations that support applications for research (e.g., new test articles or indications) or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products, are regulated by the FDA human subjects' protections.
      b. The Common Rule applies to all human subjects research conducted or sponsored by DHHS; however, typically an institution conducting any DHHS-sponsored research agrees to uphold the common rule for all research, even if it is non-sponsored.
   3. An IRB is a committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. It is composed of at least five members with varying backgrounds to promote the complete and adequate review of research activities while adhering to institutional commitments and regulations, applicable law, and standards of professional conduct and practice.
      a. The committee must be sufficiently qualified through the experience, expertise, and diversity of its members—including race, gender, cultural background, and sensitivity to such issues as community attitudes—to promote respect for its advice and counsel.
      b. At least one member should be primarily concerned with scientific areas.
      c. At least one member should be primarily concerned with nonscientific areas.
      d. At least one member should be unaffiliated with the institution and not an immediate family member of a person affiliated with the institution.
      e. IRBs assessing clinical investigations regulated by the FDA human subjects' protections must register, be subject to inspection by CDER, and follow FDA regulations.

C. IRB Approval
   1. IRB approval is required for interventional and observational studies, and applications must be reviewed annually.
   2. Research exempt from FDA IRB requirements: Emergency use of a test article is permitted on a single-use basis but must be reported to the IRB review within 5 business days of use.

3. Research exempt from DHHS IRB requirements:
    a. Research conducted in established or commonly accepted educational settings, involving normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction, such as:
        i. Educational research on instructional strategies, on the effectiveness of or the comparison between instructional techniques, curricula, or classroom management methods
        ii. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observation of public behavior (including video or audio recording), if at least one of the following is met:
            (a) Obtained information cannot be readily identified.
            (b) Any disclosure of the human subjects' responses outside the research could not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
            (c) If obtained information is identifiable, the IRB conducts a limited IRB review.
        iii. Research involving benign behavioral interventions in which information is collected from an adult subject through verbal or written responses or audiovisual recording (if the subject prospectively agrees) and at least one of the following criteria is met:
            (a) Obtained information cannot be readily identified.
            (b) Any disclosure of the human subjects' responses outside the research could not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation
            (c) If obtained information is identifiable, the IRB conducts a limited IRB review.
        iv. Secondary research that uses identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
            (a) Identifiable private information or identifiable biospecimens are publicly available
            (b) Obtained information cannot be readily identified
            (c) The research involves only information collection and analysis is regulated under HIPAA
            (d) The research is conducted by, or on behalf of, a federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with federal privacy laws
        v. Federal research or demonstration projects that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs. Each agency must maintain a public list of these projects, to be published before the research is conducted.
        vi. Taste and food quality evaluation and consumer acceptance studies.
4. Research requiring limited review:
    a. Research involving identifiable private information or identifiable biospecimens for secondary research, or storage and maintenance for future secondary research, will require broad consent and be subject to a limited review.
    b. Individual research results may not be returned to subjects as part of the study plan.

D. Research involving no more than minimal risk, and minor changes made to approved research protocols, may be considered for expedited review under both FDA and DHHS regulations.

E. The HIPAA Privacy Rule: Supplements and expands the Common Rule regulation of human subjects research to protect the confidentiality of PHI used in clinical practice, research, and the operation of health care facilities

1. PHI includes information that:
   a. Is created or received by a covered entity, which includes health care providers, hospitals, insurance companies, and business associates
   b. Pertains to the past, present, or future physical or mental health, or condition of the individual
   c. Pertains to payment for the individual's health care
   d. Pertains to the provision of health care in the past, present, or future
   e. Identifies an individual or could be used to identify an individual
2. For PHI to be used or disclosed for research purposes, one or more of the following must be obtained:
   a. Written authorization specifically for the use and disclosure of PHI for research purposes involving human subjects
   b. Waiver of authorization approved by an IRB: Use of de-identified information or limited data sets (limited data set [45 CFR §164.514(e)] defined for research, public health, and health care operations)
   c. Preparatory to research certifications
   d. Database registration
3. A provision within HIPAA also mandated adoption of a standard unique identifier for health care providers. The National Plan & Provider Enumeration System of CMS collects information from providers and assigns each a unique National Provider Identifier.

F. Examples of typical documents submitted to the IRB for an initial review can be found at NIH's National Institute on Aging Clinical Study Investigator's Toolbox (Box 8).

Box 8. Documents That May Need to Be Submitted to an IRB for Initial Review

Cover sheet	Recruitment materials
Conflict of interest assessment	Surveys, questionnaires, other instruments
Application	Federal grant, if applicable
Formal protocol	Documentation of IRB approval from another institution
Informed consent forms	Data and safety monitoring plan
HIPAA authorization forms	Additional supportive documents as requested by IRB

HIPAA = Health Insurance Portability and Accountability Act of 1996; IRB = institutional review board.

G. Informed consent
   1. Informed consent is the acknowledgment by the patient or study participant that he or she is aware of the risks and key facts of a clinical trial before deciding whether to participate. An informed consent document describes the rights of the study participants and includes details about the study.
   2. Informed consent documentation includes:
      a. A concise, focused, and comprehensible presentation of key information to aid decision-making
      b. A description of the purpose of the research
      c. The expected duration of the subject's participation
      d. A description of the required procedures
      e. A description of any reasonably foreseeable risks or discomforts to the subject
      f. A description of any benefits to the subject or to others that may reasonably be expected from the research
      g. A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject
      h. A statement describing the extent to which confidentiality of records identifying the subject will be maintained

i. A statement describing whether identifiable private information or identifiable biospecimens may or may not be used for secondary research without informed consent
j. For research involving more than minimal risk, an explanation of whether there is any compensation and an explanation of whether any medical treatments are available if injury occurs and, if so, what they consist of and where further information may be obtained.
k. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are no greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
l. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and of whom to contact in the event of a research-related injury to the subject
m. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
n. If applicable, statements addressing use of biospecimens for profit, whether results will be disclosed to participants, and whether the research includes whole-genome sequencing

3. Broad informed consent for the storage, maintenance or secondary research use of identifiable private information or identifiable biospecimens, includes additional statements regarding: a general description of the types of research that may be conducted; whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research; a description of the period of time the information or specimen may be used for research purposes; whether participants will be notified of any research uses; whether results will be disclosed to participants; an explanation of whom to contact; a statement that participation in voluntary.
4. Waivers of informed consent will only be considered for DHHS regulated research if:
   a. Research involves no more than minimal risk to subjects
   b. The waiver or alteration will not adversely affect the rights and welfare of subjects
   c. The research could not practicably be carried out without the waiver or alteration
5. When appropriate, the subjects will be provided with additional pertinent information after participation.

VIII. INVESTIGATIONAL DRUG SERVICE

A. Investigational Drug Service (IDS)
   1. The ASHP Policy on Institutional Review Boards and Investigational Use of Drugs (0711) strongly supports pharmacists' management of the control and distribution of drug products used in clinical research.
   2. The purpose of an IDS is to procure, manage, prepare, dispense, and dispose of investigational drugs in accordance with protocol and in compliance with the state and federal requirements that govern investigational drug activities.
   3. Drugs, as defined by the FD&C Act, are "(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals" (FD&C Act, sec. 201(g)(1)). An investigational drug is a chemical or biologic substance that has been tested in a laboratory and been approved by the FDA for testing in human subjects. An investigational (also referred to as experimental) drug may be:
      a. A new chemical or compound that has not been approved by the FDA for general use
      b. An approved drug undergoing further investigation for an approved or unapproved indication, dose, dosage form, or administration schedule or under an INDA in a controlled, randomized, or blinded clinical trial

4. In addition to the regulations outlined by the Office for Human Research Protections (Common Rule) and the FDA to conduct research in accordance with the principles of good clinical practice and human subject protection, an IDS has federal and state requirements.
    a. The Joint Commission standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution.
    b. The U.S. EPA and the Occupational Safety and Health Administration regulate the disposal of investigational drugs.
    c. ASHP provides practice standards.
    d. The local IRB has its own requirements.
    e. State-specific laws may vary.
5. Study-specific notebook: The notebook is maintained where study drugs are stored. It contains the files and contents listed in Table 4.

Table 4. Example of Documents Stored in Study-Specific Notebooks Maintained by an Investigational Drug Service

File Section	Contents
Protocol	Copy of the research protocol
Drug information	Investigator's brochure, drug data sheet, package inserts (if commercially available)
Pharmacy procedures	Study-specific pharmacy procedure information
Logs, forms, and labels	Study-specific materials
Procurement details	Receipt and disposition records
Correspondence	Correspondence
Computer matters	Copies of order entry codes
Billing	Financial agreements with investigator
IRB	IRB submission application, approval, and consent forms
Miscellaneous	Miscellaneous documentation
Master patient log	Record of patients enrolled
Drug accountability records	Data accountability record for each drug, dosage form, package size, and strength

IRB = institutional review board.

1. An investigational drug pharmacist's duties may include:
    a. Participating on an IRB as a voting member
    b. Maintaining a working relationship with the IRB, P&T committee, principal investigators, and the pharmacy department
    c. Reviewing new and existing investigational drug study protocols
    d. Meeting with investigators, study monitors, and other study personnel responsible for coordinating the logistics of a clinical trial
    e. Receiving, organizing, and maintaining the contents of study notebooks
    f. Providing randomization, blinding, or control functions of a clinical trial
    g. Conducting the training of IDS staff and personnel regarding investigational protocols and study drug procedures

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A
The 21st Century Cures Act authorized an increase in funding to be provided to the NIH. This funding, however, is discretionary and will need annual congressional approval through the Appropriations committees in the House and Senate, making Answer A correct. The two Appropriations committees, responsible for funding agencies of the U.S. government, include several subcommittees, among them the subcommittees on Labor, Health and Human Services, and Education and Related Agencies. The House Energy & Commerce and Senate HELP committees are responsible for regulations governing public welfare, including the HHS, NIH, FDA, CDC, and AHRQ, making Answers B & C incorrect. The House Ways & Means and Senate Finance committees are responsible for tax legislation affecting Medicare/Medicaid and CHIP, making Answer D incorrect.

2. Answer: C
Research involving human subjects is regulated by the Office for Human Protections within DHHS, making Answer A incorrect. HIPAA provisions to protect protected health information are enforced by the Office for Civil Rights within DHHS, making Answer B incorrect. The diversion of controlled substances and monitored chemicals is the responsibility of the Drug Enforcement Agency, an executive agency under the Department of Justice, making Answer C correct. The U.S. Food and Drug Administration's Office of Regulatory Affairs, which inspects regulated products and manufacturers, falls under DHHS, making Answer D incorrect.

3. Answer: C
Traditional compounders fall under Section 503A of the DQSA and outsourcing facilities under Section 503B. Outsourcing facilities, but not individual compounders, must register with the FDA, are subject to inspection by the FDA, and must report on compounded products and bulk ingredients to the secretary every 6 months, making Answer A incorrect. Similarly, outsourcing facilities, but not traditional compounders, must follow good manufacturing practices for compounding and are exempt from track-and-trace requirements, making Answers B and C incorrect. Traditional compounders must follow USP guidance for compounding, must compound products for an identified individual patient, and must follow track-and-trace requirements, making Answer C correct and, furthermore, making Answer D incorrect.

4. Answer: A
The Safe and Secure Drug Disposal Act of 2010 authorized the DEA, not DHHS, to promulgate rules for patient disposal of unused controlled substances and controlled substance disposal by long-term care facilities, making Answer B incorrect. It authorizes manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with on-site pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies, to become collectors but does not require it, making Answer D incorrect and Answer A correct. Although specified entities are permitted to reverse distribute in certain circumstances, they need not be registered as reverse distributors, making Answer C incorrect.

5. Answer: A
The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 represents a shift in reimbursement from fee-for-service to pay-for-performance or pay-for-value. It created two primary reimbursement programs: alternative payment models (APMs) and a merit-based incentive payment system (MIPS) for eligible providers, making Answer A correct. This legislation also replaces three existing value-based payment adjustments: the Physician Quality Reporting System, the Value-Based Payment Modifier, and the EHR incentive program ("meaningful use"), making Answer B incorrect, and combines them into MIPS. The American Recovery and Reinvestment Act of 2009 includes the Health Information Technology for Economic and Clinical Health (HITECH) Act, which established the program now known as "meaningful use." The Affordable Care Act created an optional Medicaid State Plan benefit that allows states to establish Health Homes to provide comprehensive care for Medicaid patients with chronic conditions and created the CMS Innovation Center to develop new care models, making Answers C and D incorrect.

6. Answer: B

The INDA is used for a new drug, a new indication, or off-label use that will be used in a clinical investigation's preclinical development for that new drug to be distributed across state lines before undergoing full FDA review. An INDA is drafted and submitted to the FDA after a preclinical study, before a phase I clinical trial, when the IND is first introduced into human subjects, making Answer B incorrect and Answers A, C, and D incorrect. The application must contain a general plan of investigation, drug information (i.e., chemistry, pharmacology, toxicology, pharmacokinetics, biologic disposition, laboratory and animal testing data, and existing human data), protocol, and manufacturing and control of the drug. An NDA is submitted after phase III studies, before market approval, making Answer D incorrect.

7. Answer: D

ANDAs, not NDAs, for generic drugs are submitted to the FDA's Center for Drug Evaluation and Research after 3–5 years of market exclusivity, making Answer A incorrect. Drug manufacturers are required to demonstrate bioequivalence equivalence, but not therapeutic equivalence, in their ANDA for a generic drug, as outlined in the Hatch-Waxman Act, making Answer B incorrect. Once the ANDA has been approved, the generic and brand manufacturer retain a 180-day exclusivity period during which the FDA may not approve other ANDAs for the same drug product, making Answer C incorrect. During this time, the brand manufacturer is producing an authorized generic. An authorized generic is produced by the brand company under the NDA but marketed as a generic, making Answer D correct. It is identical to the brand-name drug except for labeling, packaging, product/labeler code, trade name, or trademark.

8. Answer: D

Products with an A rating are both pharmaceutical equivalents and bioequivalents and can be interchanged, making Answer A incorrect. Products with a B rating are pharmaceutical equivalents only and cannot be interchanged, making Answer C incorrect. Interchangeable products must also be pharmaceutical equivalents and may therefore vary in their release mechanism or excipients but not in their dosage form or route of administration, making Answer B incorrect and Answer D correct.

9. Answer: D

The FDA requires manufacturers, packers, and distributors of marketed prescription drug products to establish and maintain records and to make reports to the FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products. Form FDA 3500 is for voluntary reporting by health care professionals, consumers, and patients, whereas 3500A is the form that must be submitted by IND reporters, manufacturers, distributors, importers, and facility personnel, making Answer D correct and Answer A incorrect. Manufacturers, packers, and distributors should not include the names and addresses of individual patients. However, health care providers may continue to make adverse event reports under the HIPAA Privacy Rule. The HIPAA Privacy Rule is not intended to disrupt or discourage adverse event reporting in any way. In fact, the Privacy Rule specifically permits covered entities (e.g., pharmacists, physicians, hospitals) to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products, both to the manufacturers and directly to the FDA. As an explanation, the following statement has been provided: "The HIPAA Privacy Rule recognizes the legitimate need for public health authorities and others responsible for ensuring public health and safety to have access to PHI to carry out their public health mission. The rule also recognizes that public health reports made by covered entities are an important means of identifying threats to the health and safety of the public at large, as well as individuals. Accordingly, the rule permits covered entities to disclose PHI without authorization for specified public health purposes." However, names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in adverse drug experience reports are not releasable to the public under the FDA's public information regulations, making Answer C incorrect. Answer B is incorrect because consumers and patients should complete Form 3500B.

10. Answer: B

A warfarin order dispensed to the wrong patient is considered a medication error, and it does not appear to have caused harm, making Answer A incorrect. Hemorrhage caused by heparin use is considered an adverse drug event and should be reported, making Answer B correct. Hospitalization of a patient who takes too much

insulin because of a prescribing error is considered a preventable adverse drug event and does not need to be reported, making Answer C incorrect. Development of hives in a patient taking cephalexin is considered an adverse drug reaction and does not need to be reported, making Answer D incorrect.

11. Answer: C

The NCQA, not the Joint Commission, is responsible for developing and maintaining the HEDIS that health plans use to measure performance and focus improvement efforts, making Answer A incorrect. The Agency for Healthcare Research and Quality developed the HCAHPS survey, which measures the consumer experience with health care and can be used to make quality assessments for programs such as value-based purchasing. The PCORI supports and funds comparative clinical effectiveness research, making Answer B incorrect. The Joint Commission is responsible for developing and maintaining the National Hospital Quality Measures as a part of its ORYX initiative to integrate outcomes and accountability into core measures, making Answer D incorrect. The NQF endorses national consensus standards for measuring and publicly reporting on performance, making Answer C correct.

12. Answer: B

CFR Title 21 Part 56 contains standards for the composition, operation, and responsibility of an institutional review board (IRB) and regulates human subjects research that involves an investigational drug or device and use of approved products in investigations, making Answer A incorrect. CFR Title 45 Part 46 protects human subjects involved in research conducted or sponsored by any agency within the DHHS, making Answer B correct. Exemptions to DHHS IRB review are granted for specific types of educational, behavioral, secondary, and federal research, making Answer C incorrect. Written authorization would be required specifically for the use and disclosure of PHI for research purposes or a waiver of authorization for use of de-identified information or limited data sets, making Answer D incorrect.

13. Answer: B

Research involving no more than minimal risk, and minor changes made to approved research protocols, may be considered for expedited review, not exempt review, making Answer A incorrect. Waivers of informed consent may be considered if the research involves no more than minimal risk, the research cannot be conducted without the waiver, and the waiver does not negatively affect patient rights and welfare, making Answer C incorrect. Specific types of educational research, surveys, interviews, or observations of public behavior that cannot be linked to subjects in any way and whose disclosure could not reasonably expose subjects to adverse consequences, or research involving existing data or specimens that are publicly available or cannot be linked to subjects in any way, may be exempt from IRB requirements, making Answer D incorrect. Answer B is correct because use of de-identified information or limited data sets requires a PHI waiver of authorization.