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. Describe the regulatory actions that govern the prescription drug approval process and human subjects research.
3. Identify the regulatory and oversight bodies with jurisdiction over health system delivery of care.
4. Describe national quality initiatives aimed at improving health care delivery and patient health outcomes.
5. Explain medication policy implications at an institutional level.

Self-Assessment Questions

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

1. With respect to reporting for adverse drug experiences, which is the best option to correctly describe the purpose of MedWatch Form FDA 3500A?
   A. Is for voluntary reporting by health care professionals of a serious adverse event, product quality problem, or product use error with a U.S. Food and Drug Administration (FDA)-regulated drug, biologic, medical device, or dietary supplement.
   B. May contain patient identifiers and still comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.
   C. Is the mandatory form to be submitted by investigational new drug (IND) reporters, manufacturers, distributors, importers, and facility personnel.
   D. Is for consumer reporting of adverse drug experiences.

2. When considering the generic drug approval process, which choice is best to correctly define a generic drug?
   A. Follows the Accelerated New Drug Application regulatory pathway for approval.
   B. Must be bioequivalent to the branded product.
   C. Must be therapeutically equivalent to the branded product.
   D. Will be rated “A” in the Orange Book if it is not therapeutically equivalent.

3. If a medication guide is part of a Risk Evaluation and Mitigation Strategies (REMS) program as an element to ensure safe use, which option best describes it?
   A. Must be provided when a drug is dispensed in an outpatient setting and will be used without direct supervision by a health care professional.
   B. Does not need to be provided to a hospital inpatient receiving that drug.
   C. Cannot be removed from that REMS program in the future.
   D. Does not need to be provided when a drug is dispensed to a health care professional for administration to a patient in an outpatient setting.

4. Which option is best to correctly state when an IND application should be submitted to the FDA?
   A. Before preclinical studies.
   B. After preclinical studies, before phase I clinical trials.
   C. During phase II studies.
   D. After phase III studies, before market approval.

5. Which is the best choice for correctly defining a phase II clinical trial?
   A. A study that tests a new drug or treatment on a few subjects for the first time.
   B. A preliminary study of the intervention’s efficacy that compares it with an existing intervention or placebo.
   C. A study that evaluates a drug or intervention on a larger sample of subjects and assesses efficacy and adverse effects.
   D. A study consisting of postmarketing studies to obtain additional information about risks, benefits, and best use recommendations.
6. Which is the best choice to correctly describe what 45 Code of Federal Regulations (CFR) Part 46 pertains to?
   A. Health Insurance Portability and Accountability Act.
   B. Bioavailability and bioequivalence requirements.
   C. The Vaccine Injury Compensation Program.

7. Which is the most accurate definition of an adverse drug reaction?
   A. Injury from a medication that did not result from a medication error and was not preventable.
   B. Injury caused by medication use.
   C. Injury caused by a medication error.
   D. Injury potential because of a medication error.

8. If a high-risk compounded sterile product (CSP) has not undergone sterility testing, which is the most appropriate choice of beyond-use date if it is stored in a freezer?
   A. 14 days.
   B. 15 days.
   C. 30 days.
   D. 45 days.

9. Which option is best to correctly name the legislative act that created an abbreviated FDA approval pathway for generic drugs?
   C. Durham-Humphrey Amendment of 1951.
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 patient care delivery and clinical research activity. Specifically, this chapter addresses rules, regulations, and quality initiatives starting at the national level and closing at the institutional level.

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

A. Basics
   1. Congress is bicameral, with two legislative chambers.
      a. The Senate is composed of 100 elected, voting members.
         i. Legislation and tasks are divided into 16 standing committees, 72 subcommittees, 4 special committees, and 4 joint committees. The committees that have jurisdiction over health-related policy include the following:
            (a) Appropriations Committee writes the legislation that allocates federal funds to the numerous government agencies, departments, and organizations on an annual basis and, in particular, funds discretionary programs.
            (b) Finance Committee 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.
            (c) 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).
            (d) Committee on Veterans’ Affairs oversees issues related to veterans’ affairs.
         ii. Legislation is reviewed by the committee with the most jurisdiction over the provisions in the bill.
      b. The House of Representatives is composed of 435 elected, voting members and six delegates from the U.S. territories or from Washington, DC, with nonvoting privileges.
         i. Legislation and tasks are divided into 20 standing committees and 4 joint committees. The committees with jurisdiction over health-related policy include the following:
            (a) Appropriations has jurisdiction similar to that listed above.
            (b) Ways and Means has jurisdiction over taxation and most programs authorized by the Social Security Act and is similar to the Senate Finance Committee.
            (c) Energy and Commerce is the oldest standing committee of the House of Representatives, has oversight of the DHHS and is similar to the Senate HELP committee.
            (d) Veterans’ Affairs oversees issues related to veterans’ affairs.
         ii. Legislation is sent to any committee that has jurisdiction over any of the provisions in the bill.

2. Legislative process (Figure 1)
   a. 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.
   b. Once introduced, the bill, joint resolution, concurrent resolution, or simple resolution 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.
B. Definitions
1. Authorization bills grant authority for a program or agency to exist.
2. Appropriation is a sum of money designated for a particular purpose by an act or bill.
3. Entitlement spending for programs such as Medicare, Medicaid, and Social Security is automatically set according to eligible recipients. Levels of spending can be changed only by eligibility criteria changes.
4. Discretionary spending represents annual spending levels determined by Congress; such spending is optional.
5. Continuing resolution continues funding for a program if the congressional fiscal year, ending September 30, ends without a new appropriation in place.

C. Recent Legislative Activity with Regulatory Policy Implications
1. The American Recovery and Reinvestment Act (ARRA) of 2009 provided a vehicle for passing the Health Information Technology for Economic and Clinical Health (HITECH) Act. The HITECH Act authorizes the U.S. DHHS to create programs to improve health care quality, safety, and efficiency through the promotion of health information technology, including electronic health records (EHRs).
   a. Created the Office of the National Coordinator to coordinate nationwide 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. The Incentive Program for Electronic Health Records was issued by the Centers for Medicare & Medicaid Services (CMS) to provide a financial incentive to eligible professionals, eligible hospitals and critical access hospitals, and Medicare Advantage Organizations that are “meaningful users” of EHRs. ARRA 2009 specified three main components for “meaningful use”:
      i. Use of certified EHRs in a meaningful manner (e.g., e-Prescribing)
      ii. Use of certified EHR technology for electronic exchange of health information to improve the quality of health care
      iii. Use of certified EHR technology to submit clinical quality and other measures

Figure 1. Legislative process.
d. Incentive payments began in fiscal year 2011 and will gradually decrease until fiscal year 2015, when penalties are put into effect.
e. HITECH also affects research because it imposes new penalties for breaches in HIPAA and protected health information (PHI); the Office for Civil Rights within the DHHS will audit for compliance.

2. 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. As the law translates into regulation, unique opportunities exist for pharmacists to become engaged.
   a. Funding opportunities will be available for pharmacists to show their contributions as providers of medication therapy management.
   b. The patient-centered medical home model emphasizes primary care as a central role in managing the chronic conditions of patients using a team-based care approach.
   c. Accountable Care Organizations (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.
   d. The Independence at Home Demonstration Program promotes the interdisciplinary collaboration of clinicians to provide home-based medical care for Medicare beneficiaries.
   e. The Biologics Price Competition and Innovation Act of 2009 is a provision in the ACA that creates an abbreviated approval pathway for follow-on biologic products, known as “biosimilars.”
   f. The Physician Payments Sunshine Act (i.e., Sunshine Act) requires 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.
      i. CMS authorized to implement the Sunshine Act as the Open Payments Program
      ii. Reports on 2013 data were released in September 2014.

3. The Safe and Secure Drug Disposal Act of 2010
   a. Authorized the Drug Enforcement Administration (DEA) to promulgate rules for patient disposal of unused controlled substances and controlled substance disposal by long-term care facilities
   b. The Disposal of Controlled Substances Final Rule, published on September 9, 2014, and enacted on October 9, 2014, 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.
      i. Authorized collectors include manufacturers, distributors, reverse distributors, narcotic treatment programs, hospitals and clinics with onsite pharmacies, and retail pharmacies, including long-term care facilities and specialty pharmacies.
      ii. Allows ultimate users to voluntarily dispose of controlled substances through take-back events, mail-back events, and collection receptacles.
      iii. Regulates each element of the disposal process, including transfer, deliver, collection, return, and recall of controlled substances

4. The Food and Drug Administration (FDA) Safety and Innovation Act of 2012 amends the federal Food, Drug, and Cosmetic (FD&C) Act to revise and extend the user fee programs for prescription drugs and medical devices to establish user fee programs for generic drugs, biosimilars, and other purposes.
   a. 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 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
b. 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.

5. The Drug Quality and Security Act of 2013
   a. Establishes a new section in the FD&C Act to allow a compounding facilities to voluntarily register as “outsourcing facilities” with the FDA. The outsourcing facility must give a licensed pharmacist direct oversight over compounded drugs, compound drugs only with bulk ingredients listed as approved by the secretary, report to the secretary every 6 months, undergo inspection by the FDA, report serious adverse events, and label products identifying them as a compounded drug.
   b. Adds a new section to the FD&C Act with product-tracing requirements (“track-and-trace”) for drug manufacturers, repackers, wholesale distributors, and dispensers to provide transaction details when pharmaceutical products change ownership. Entities will also need to respond promptly in the event of a recall or an illegitimate product suspicion or investigation.
   c. Increases wholesale distributor licensure standards

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

A. DHHS is the agency charged with protecting the health of Americans. Appropriations to DHHS represent the largest share of nondefense discretionary funding, at 32% of federal monies appropriated.
   1. The FDA is responsible for the safety of most foods (human and animal) and cosmetics, and it regulates both the safety and effectiveness of human drugs, biologics (e.g., vaccines, blood products, therapeutic proteins), medical devices, and animal drugs.
   2. The CMS administers Medicare, Medicaid, and the State Children’s Health Insurance Program. It is driving the Value-Based Purchasing Program, the Medicare Shared Savings Program, and the 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.
   4. The Centers for Disease Control and Prevention (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.

B. U.S. Department of Justice (DOJ): Has jurisdiction over the DEA, which prevents, detects, and investigates the diversion of controlled substances and monitored chemicals.

C. Departments and agencies of the U.S. government make rules and adjudicate (enforce) them within areas of delegated authority.
   1. The Administration Procedure Act of 1946 granted agencies of the DHHS the power to promulgate rules and regulations that have the effect of substantive law.
   2. Codification of general and permanent rules is published in the Federal Register, and the public is allowed to provide feedback within a prespecified time limit.
a. Example: DHHS CMS 42 Code of Federal Regulations (CFR) parts 424 and 431: Medicare and Medicaid Programs; Changes in Provider and Supplier Enrollment, Ordering and Referring, and Documentation Requirements; and Changes in Provider Agreements. This final rule expanded the definition of nonphysician practitioners on hospital staffs to include pharmacists.

b. Example: DOJ DEA 21 CFR Parts 1300, 1301, 1304, et al: Disposal of Controlled Substances; This final rule governs the secure disposal of controlled substances by DEA registrants and ultimate users.

3. Final rules are published in the CFR, which has 50 titles; they are updated every year on a staggered basis.
   a. Title 21: Food and Drugs  
   b. Title 37: Patents, Trademarks, and Copyrights  
   c. Title 42: Public Health  
   d. Title 45: Public Welfare  
         (a) Defines research as a systematic investigation, including research, development, testing, and evaluation, designed to develop or contribute to generalizable knowledge  
         (b) Defines a human subject as a living individual about whom an investigator obtains data through intervention or interaction with the individual or identifiable private information  
      ii. HIPAA (45 CFR Part 160 and subparts A and E of 164)

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

A. Basics

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. The FDA is funded through discretionary spending every fall in Congress’s 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.

2. It is organized by the Office of the Commissioner and the four directorates that oversee the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations. The following offices and centers affect medication use:
   a. Office of the Commissioner conducts overall agency coordination; the FDA’s top official, the commissioner, requires Senate confirmation.
   b. Office of Regulatory Affairs, the largest office, regulates all inspection and enforcement activities.
   c. National Center for Toxicological Research supports the six product centers with scientific technology, training, and technical expertise.
   d. Center for Drug Evaluation and Research (CDER) regulates prescription and nonprescription drugs.
   e. Center for Biologics Evaluation and Research regulates biologic products, including vaccines, blood products, and gene therapy.
   f. Center for Devices and Radiological Health regulates medical devices.
   g. Center for Food Safety and Applied Nutrition regulates most foods, food additives, infant formulas, dietary supplements, and cosmetics.
   h. Center for Tobacco Products regulates tobacco-containing products.
   i. Center for Veterinary Medicine regulates feed, drugs, and devices used for pets, farm animals, and other animals.
B. Definitions

1. The *Abbreviated New Drug Application* (ANDA) contains data that, when submitted to the FDA’s CDER, Office of Generic Drugs, allow the review and ultimate approval of a generic drug product.

2. 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, or trademark differs from that of the listed drug.

3. A *biologics license application* is a submission that 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) seeking approval to market in the United States.

4. 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 required by the FDA seek to determine whether new drugs or treatments are both safe and effective.

5. The interchangeability of a biosimilar product allows 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.

6. An *Investigational New Drug Application* (INDA) is used 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 new drug to be distributed across state lines before full FDA review.

7. A *New Drug Application* (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States.

C. 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 Hygienic Laboratory, precursor of the National Institutes of Health (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 Pharmacopoeia and the National Formulary (USP/NF) as official standards for drugs

4. The FD&C 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 for drug firms to demonstrate efficacy as well as safety
   b. 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., 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 for a patient population of less than 200,000.


10. The Food and Drug Administration Act of 1988: Officially established the FDA as an agency in the DHHS.

   a. Requires drug, biologics, and medical device (Medical Device User Fee Amendments) manufacturers to pay fees for product applications, supplements, and other services.


13. The FDA Modernization Act of 1997
   a. Streamlines clinical research on drugs and devices.
   b. Has 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.
      i. Provides abstracts of clinical study protocols that investigators are required to submit.
         (a) Summary and purpose of study.
         (b) Recruiting status.
         (c) Criteria for patient participation.
         (d) Location for trial and specific contact information.
         (e) Research study design.
         (f) Phase of trial.
         (g) Disease or condition and drug or therapy under study.
      ii. More than 179,620 clinical trials have been listed with locations in all 50 states and in 187 countries.

   a. Vehicle for reauthorizing PDUFA.
   b. Statutory authority to require Risk Evaluation and Mitigation Strategies (REMS).
   c. Expanded the requirements for the types of drugs that must be registered on ClinicalTrials.gov; requires the submission of results for certain clinical trials.


16. The Biologics Price Competition and Innovation Act, passed as a provision within the ACA: Established a regulatory approval pathway for biosimilars or follow-on biologics.

17. The Reducing Prescription Drug Shortages Executive Order was signed by President Barack Obama on October 31, 2011. It 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 to avoid or mitigate existing or potential drug shortages. Reviews may include new drug suppliers, manufacturing sites, and manufacturing changes.
   c. Communicate to the DOJ any evidence of or behaviors by market participants that have contributed to stockpiling or exorbitant prices.
18. The FDA Safety and Innovation Act of 2012
   a. Reauthorized PDUFA
   b. See section I.C.3.
19. The Drug Quality and Security Act of 2013 (see section I.C.4.)

D. Prescription Drug Approval Path
1. Preclinical studies
   a. Laboratory and animal studies that assess safety and biologic activity in various model systems
      i. ED$_{50}$ is the amount of drug that produces a specific effect in 50% of animals tested.
      ii. LD$_{50}$ is the amount of drug that causes death in 50% of animals tested.
   b. Toxicologic studies completed
      i. Effects on the fetus in pregnant mice, rats, rabbits, or baboons
      ii. May or may not translate into human fetal adverse effects
      iii. Fetal effects in humans may occur that were not observed in animal studies.
      iv. Basis for pregnancy categories B, C, and some D
   c. 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.
2. Phase I drug trial
   a. Initial introduction of an IND into humans, typically 20–80 healthy volunteers
   b. 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.
3. Phase II drug trial
   a. Controlled clinical studies conducted in no more than several hundred subjects
   b. 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.
4. Phase III drug trial
   a. Involves administering the investigational drug to a range of several hundred to several thousand patient subjects in different clinical settings to confirm its safety, efficacy, and appropriate dosage
   b. Goal is to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
   c. The step before the sponsor’s submission of an NDA to the FDA for approval to market the drug
   d. Once an NDA is submitted, it is classified with a code that reflects both the type of drug being submitted and its intended uses. The numbers 1–7 are used to describe the type of drug:
      i. New molecular entity (1)
      ii. New salt of previously approved drug (2)
      iii. New formulation of previously approved drug (3)
      iv. New combination of two or more drugs (4)
      v. Already marketed drug product (i.e., new manufacturer) (5)
      vi. New indication for currently marketed drug or switch from prescription to over the counter (6)
      vii. Already marketed drug product without a previously approved NDA (7)
   e. Letter code describes the review priority of the drug.
      i. S = standard review for drug similar to currently available drugs.
      ii. P = priority review for drugs that represent significant advances over existing treatments.
   f. Not all phase III drugs are approved, and the FDA can impose a clinical hold at any stage.
Table 1. Components of the New Drug Application

<table>
<thead>
<tr>
<th>Index</th>
<th>Nonclinical pharmacology and toxicology</th>
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<tbody>
<tr>
<td>Summary</td>
<td>Human pharmacokinetics and bioavailability</td>
</tr>
<tr>
<td>Chemistry, manufacturing, and control</td>
<td>Microbiology (for antimicrobial drugs only)</td>
</tr>
<tr>
<td>Samples, methods, and labeling</td>
<td>Clinical data</td>
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<tr>
<td>Safety update report</td>
<td>Case report forms</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Patent information</td>
</tr>
<tr>
<td>Case report tabulations</td>
<td>Patent certification</td>
</tr>
<tr>
<td>Other pertinent information</td>
<td></td>
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</tbody>
</table>

aNDA = New Drug Approval.

bThe safety update report is usually submitted 120 days after the NDA submission.

5. Phase IV drug trial
   a. Also called postmarketing studies
   b. May be required by the FDA to identify additional information about the drug’s risks, benefits, and optimal use
   c. Verify effectiveness or focus treatment on special populations

E. Generic Drugs
1. In 2012, 77% of all drugs dispensed were generic.
2. A generic drug product is identical to an innovator drug product in active ingredient, dosage form and strength, route of administration, quality, and intended use. It must also demonstrate bioequivalence, showing there are no significant differences in the rate and extent of absorption of the therapeutic ingredient. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, defined bioequivalence statutorily as a means to approve a generic drug.
3. Once an ANDA is submitted to and approved by CDER's Office of Generic Drugs, the applicant can manufacture and market the generic drug as a safe, effective, and low-cost option to the public.
4. All approved multisource products are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). The therapeutic equivalence coding system, using A or B, helps health care providers determine whether the FDA evaluated a product to be therapeutically equivalent to other pharmaceutically equivalent products.
   a. A code: an approved generic product considered to be therapeutically equivalent to other pharmaceutical equivalents
   b. B code: an approved generic product that is not considered to be therapeutically equivalent to other pharmaceutical equivalents
5. ANDAs generally do not require preclinical or clinical data; rather, they must demonstrate bioequivalence.
6. Pharmaceutical equivalents
Table 2. Criteria for Medications to Be Pharmaceutical Equivalents

<table>
<thead>
<tr>
<th>Three criteria:</th>
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<tbody>
<tr>
<td>• Must contain the same active ingredient</td>
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<td>• Must be the same dosage form and route of administration</td>
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<tr>
<td>• Must be of identical strength or concentration</td>
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<table>
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<tr>
<th>Differences allowed:</th>
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<tbody>
<tr>
<td>• Shape</td>
</tr>
<tr>
<td>• Releasing mechanism</td>
</tr>
<tr>
<td>• Labeling (limited differences)</td>
</tr>
<tr>
<td>• Scoring</td>
</tr>
<tr>
<td>• Excipients (colors, flavors, preservatives)</td>
</tr>
</tbody>
</table>

7. Therapeutic equivalents can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.
   a. Criteria
      i. Pharmaceutical equivalent
      ii. Therapeutic equivalence codes rated “A” by the FDA
      iii. Designates a brand-name drug or a generic drug as the reference-listed drug
      iv. Demonstrates bioequivalence
   b. Assigns therapeutic equivalence code according to data submitted in an ANDA to demonstrate bioequivalence
      i. An ANDA contains adequate scientific evidence, established through in vivo or in vitro studies, of bioequivalence of the product to the reference-listed drug.
      ii. Products deemed by the FDA not therapeutically equivalent are rated “B.”

8. An authorized generic is a drug that is produced by the brand company under the NDA but marketed as a generic, and a regular generic is produced under an ANDA. It is identical to the brand alternative in both active and inactive ingredients. The Federal Food, Drug, and Cosmetic Act establishes an 180-day exclusivity period after approval of an ANDA. This is the period in which the FDA cannot approve other ANDAs for the same drug product.

9. At-risk launch of a generic occurs when a generic drug manufacturer challenges the validity of the existing patent of a brand drug.

10. Follow-on biologics or biosimilars are drugs or vaccines that have been produced in living cells.
    a. Biosimilars are approved new versions of an innovator biologic product after patent expiration. Although this is an area of controversy between the government, industry, and patient advocacy organizations, biosimilars offer a means to decrease the rapidly rising costs of biologic products.
    b. Legislation has created a statutory pathway for the FDA to approve these products after 12 years of data exclusivity for the manufacturer of a new biologic product; however, the FDA has yet to publish a final rule on the regulatory pathway for biosimilars.

11. Table 3 compares the regulatory pathway differences between small molecules and biologics for FDA approval.
Table 3. Regulatory Approval Pathway Comparison for Small Molecule and Biologic Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Regulatory Pathway</th>
<th>Nonproprietary Name</th>
<th>Indications</th>
<th>Interchangeability</th>
<th>Clinical and Trial Data Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecule (Food, Drug, and Cosmetic Act)</td>
<td>New Drug Application (505(b)1 and 2)</td>
<td>N/A; Legend (Brand) drug</td>
<td>N/A; Legend (Brand) drug</td>
<td>N/A; Legend (Brand) drug</td>
<td>Clinical data required; safety and efficacy data requirement</td>
</tr>
<tr>
<td></td>
<td>Abbreviated New Drug Application (505(j))</td>
<td>Same as originator</td>
<td>Same as originator</td>
<td>Granted with initial approval (e.g., Orange Book rating)</td>
<td>Clinical data not required; bio-equivalence data requirement</td>
</tr>
<tr>
<td>Biologic (Public Health Services Act)</td>
<td>Biologics License Application (351(a))</td>
<td>N/A; Legend (Brand) drug</td>
<td>N/A; Legend (Brand) drug</td>
<td>N/A; Legend (Brand) drug</td>
<td>Clinical data required; purity, safety, and potency data requirement</td>
</tr>
<tr>
<td></td>
<td>Biosimilar Application (351(k))</td>
<td>Uncertain, may be different</td>
<td>May or may not have all indications, extrapolation allowed</td>
<td>Possible but not upon initial approval</td>
<td>Clinical data required; abbreviated data requirement with purity, safety, and potency (i.e., totality of the evidence)</td>
</tr>
</tbody>
</table>

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 that does not achieve any of its primary intended purposes through chemical action within or on the body of human beings or other animals and that does not depend on being metabolized for the achievement of any of its primary intended purposes
2. Regulated by the Center for Devices and Radiological Health
   a. To be approved, a medical device manufacturer must submit a premarket approval application ensuring the device’s safety and efficacy.
   b. If a medical device is essentially equivalent to an existing, legally marketed device, a 510(k) is submitted for premarket notification.
   c. An investigational device exemption allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required to support a premarket approval application or a premarket notification 510(k) submission to the FDA.
3. Classified according to the risks associated with the device:
   a. Class I: Deemed low risk and therefore subject to the least regulatory control
   b. Class II: Higher-risk devices than class I that require greater regulatory controls to ensure reasonable safety and efficacy
   c. Class III: Highest-risk devices, subject to the greatest regulatory control; must be approved by the FDA before marketing
G. Risk Evaluation and Mitigation Strategies (REMS)
   1. Replaces the Risk Minimization Action Plans
   2. Requires that a drug be dispensed with one of the following:
      a. Medication guide or patient package inserts
      b. Communication plan to health care providers
      c. Elements To Assure Safe Use (ETASU) (Table 4)

<table>
<thead>
<tr>
<th>Table 4. Risk Evaluation and Mitigation Strategies’ Requirements of ETASU</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETASU may include one or more of the following:</td>
</tr>
<tr>
<td>• Health care providers who prescribe the drug have particular training or experience or are specially certified</td>
</tr>
<tr>
<td>• Pharmacies, practitioners, or health care settings that dispense the drug are specially certified</td>
</tr>
<tr>
<td>• Drug is dispensed only in certain health care settings</td>
</tr>
<tr>
<td>• Drug is dispensed to patients with evidence of safe use conditions such as laboratory test results</td>
</tr>
<tr>
<td>• Each patient using the drug is subject to monitoring</td>
</tr>
<tr>
<td>• Each patient using the drug is enrolled in a registry</td>
</tr>
</tbody>
</table>

3. 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.

4. A medication guide must be provided in all settings, including inpatient settings, outpatient settings but administered by a health care professional, and outpatient settings but dispensed to a patient, if the agent is listed as an ETASU in an REMS program.

H. Critical Path Initiative
   1. 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
   2. Prioritizes the most pressing developmental problems and identifies areas that provide the greatest opportunities for rapid improvement and public health benefit through three dimensions (Table 5)

<table>
<thead>
<tr>
<th>Table 5. The FDA’s Critical Path Initiative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimension</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Assessing safety</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Showing medical utility</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Product industrialization</td>
</tr>
<tr>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>
IV. INSTITUTIONAL REVIEW BOARD IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

A. Basics
   1. By federal regulation, every institution that conducts or supports biomedical or behavioral research involving human participants must have an institutional review board (IRB) that initially approves and periodically reviews research protocols to protect the rights of human participants.

   2. Governed by the 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, subpart A constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects.

   3. IRB approval is required for interventional and observational studies, and applications must be reviewed annually.

B. Definitions
   1. The Health Insurance Portability and Accountability Act of 1996 provides protection for the privacy of certain individually identifiable health data, or PHI.

   2. A human subject is a living person about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.

   3. Informed consent is the process of learning the key facts about a clinical trial before deciding whether to participate.

   4. An informed consent document describes the rights of the study participants and includes details about the study including purpose, duration, required procedures, risks, benefits, and key contacts.

   5. 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.

   6. 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.

C. The IRB 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.

   1. The committee must be sufficiently qualified through the experience, expertise, and diversity of its members, including race, gender, cultural background, and sensitivity to issues such as community attitudes, to promote respect for its advice and counsel.

   2. At least one member whose primary concerns are in scientific areas

   3. At least one member whose primary concerns are in nonscientific areas

   4. At least one member who is not affiliated with the institution and who is not an immediate family member of a person affiliated with the institution

D. Human Subjects Training
   1. Institution specific

   2. A Collaborative Institutional Training Initiative program is a subscription-based service that provides research ethics training to its members.

E. Research Exempt from IRB Requirements
   1. Research conducted in established or commonly accepted educational settings, involving normal educational practices such as:
      a. Research on regular or special education instructional strategies
b. Research on the effectiveness of the comparison between instructional techniques, curricula, or classroom management methods

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observation of public behavior, unless:
   a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects.
   b. Any disclosure of the human subjects’ responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.

3. Research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens; if these sources are publicly available or if the information is recorded by the investigator in a manner such that subjects cannot be identified, directly or through identifiers linked to the subjects

4. Research involving no more than minimal risk, and minor changes made to approved research protocols, may be considered for expedited review.

F. The HIPAA Privacy Rule: Supplements and expands the common rule regulation of human subjects research

1. Protections for the confidentiality of PHI used in clinical practice, research, and the operation of health care facilities

2. PHI includes information that:
   a. Is created or received by a covered entity, which includes a health care provider
   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

3. To use or disclose PHI 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 deidentified 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

4. 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.

G. Typical Documents Submitted to the IRB for an Initial Review. Examples of these documents can be found at NIH’s National Institute on Aging Clinical Study Investigator’s Toolbox (Table 6).

Table 6. Documents That May Need to Be Submitted to an IRB for Initial Review

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

HIPAA = Health Insurance Portability and Accountability Act; IRB = institutional review board.
H. Informed Consent
   1. Basic elements
      a. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject’s participation, a description of the procedures to be followed, and the identification of any procedures that are experimental
      b. A description of any reasonably foreseeable risks or discomforts to the subject
      c. A description of any benefits to the subject or to others that may reasonably be expected from the research
      d. A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject
      e. A statement describing the extent to which confidentiality of records identifying the subject will be maintained
      f. 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, or where further information may be obtained
      g. 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
      h. 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
   2. Waiver will be considered 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.
   3. When appropriate, the subjects will be provided with additional pertinent information after participation.

V. INVESTIGATIONAL DRUG SERVICE

A. Basics
   1. The American Society of Health-System Pharmacists (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 investigational drug service (IDS) is to procure, manage, prepare, dispense, and dispose of investigational drugs according to protocol and in compliance with the state and federal requirements that govern investigational drug activities.

B. Definitions: 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 to be tested in human subjects. An investigational (also referred to as experimental) drug may be:
   1. A new chemical or compound that has not been approved by the FDA for general use
   2. 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.
C. 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 subjects protection, an IDS has federal and state requirements.
   1. The Joint Commission standards require policies for the use of investigational drugs that specifically address their storage, dispensing, labeling, and distribution.
   2. The Environmental Protection Agency and Occupational Safety and Health Administration regulate the disposal of investigational drugs.
   3. ASHP provides practice standards.
   4. The local IRB has its own requirements.
   5. State-specific laws may vary.

D. Study-Specific Notebook: The notebook is maintained where study drugs are stored. It contains the files and contents listed in Table 7.

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

IRB = institutional review board.

E. In addition to managing the activities outlined under section V.A.2, an investigational drug pharmacist’s duties may include the following:
   1. Participating on an IRB as a voting member
   2. Maintaining a working relationship with the IRB, Pharmacy and Therapeutics (P&T) Committee, principal investigators, and the pharmacy department
   3. Reviewing new and existing investigational drug study protocols
   4. Meeting with investigators, study monitors, and other study personnel responsible for coordinating the logistics of a clinical trial
   5. Receiving, organizing, and maintaining the contents of study notebooks
   6. Providing randomization, blinding, or control functions of a clinical trial
   7. Conducting the training of IDS staff and personnel regarding investigational protocols and study drug procedures
VI. THE JOINT COMMISSION, NATIONAL COMMITTEE FOR QUALITY ASSURANCE, NATIONAL QUALITY FORUM, AGENCY FOR HEALTHCARE RESEARCH AND QUALITY, AND PHARMACY QUALITY ALLIANCE

A. The programs outlined in this section are not federal regulatory programs, but they play an important role in the pharmacist’s ability to provide patient-centered, safe, and effective care.

B. The Joint Commission is a not-for-profit, independent organization that sets standards for accrediting healthcare 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.”

1. Basics
   a. Accredits and certifies more than 20,500 health care organizations in the United States
   b. Standards address an organization's performance in functional areas of patient rights, patient treatment, medication safety, and infection control. Hospitals provide data from a selection of 57 inpatient measures.

2. Definitions
   a. National Patient Safety Goals were established to help accredited organizations address specific areas of concern in patient safety in the areas of ambulatory health care, behavioral health care, critical access hospital, home care, hospital, laboratory, long-term care, Medicare or Medicaid long-term care, and office-based surgery.
   b. The ORYX is a Joint Commission performance measurement and improvement initiative implemented to integrate outcomes with accountability measures in the areas of acute myocardial infarction, heart failure, 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. Common standardized measures between the Joint Commission and CMS are called National Hospital Quality Measures.
      ii. Accountability measures and processes that result in the greatest improvement in patient outcomes have been 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 and include acute myocardial infarction, heart failure, pneumonia, surgical care improvement project, children’s asthma care, venous thromboembolism, and stroke. Examples of current inpatient measures are as follows:
         (a) Acute myocardial infarction
             (1) Aspirin at arrival
             (2) Aspirin prescribed at discharge
             (3) Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for left ventricular systolic dysfunction
             (4) β-Blocker at discharge
             (5) Median time to fibrinolysis
             (6) Fibrinolytic therapy within 30 minutes of hospital arrival
             (7) Median time to percutaneous coronary intervention
             (8) Primary percutaneous coronary intervention balloon within 90 minutes of hospital arrival
             (9) Statin prescribed at discharge
(b) Children’s asthma care

1. Use of relievers for inpatient asthma using an overall rate for ages 2–17 years and divided into age ranges 2–4 years, 5–12 years, and 13–17 years
2. Use of systemic corticosteroids for inpatient asthma using an overall rate for ages 2–17 years and divided into age ranges 2–4 years, 5–12 years, and 13–17 years
3. Home management plan of care given to patient or caregiver

C. The National Committee for Quality Assurance (NCQA) is a private, not-for-profit organization with a mission to improve the quality of health care through measurement, transparency, and accountability.

1. Basics
   a. Accreditation programs, certification programs, physician recognition programs, and distinctions are directed at health plans, such as health maintenance organizations, preferred provider organizations, and consumer-directed health plans, physician networks, medical groups, and individual physicians.
   b. Responsible for three key efforts to measure and improve health care quality: assessment of on-site clinical and administrative processes (approximately 54% of NCQA measures), through data collection for the Healthcare Effectiveness Data and Information Set (HEDIS) (approximately 33% of NCQA measures), and measuring member satisfaction through the Consumer Assessment of Healthcare Providers and Systems survey (approximately 13% of NCQA measures)
   c. Produces several public reports, including “The State of Health Care Quality,” which is an 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
   d. NCQA will establish criteria for ACOs, created by the ACA. Principles of ACOs include the following:
      i. Strong foundation of primary care
      ii. Reliable reporting of measures to support quality improvement and to eliminate waste and inefficiencies to reduce cost
      iii. Commitment to improving quality and patient experience while reducing per capita costs
      iv. Collaboration with stakeholders in a community or region
      v. Creating and supporting a sustainable workforce.

2. Definitions
   a. The HEDIS is a tool that consists of more than 81 measures across five domains of care that health plans use to measure performance and focus improvement efforts.
      i. Measures are developed by identifying the clinical area to evaluate, conducting an extensive literature review, developing the measure, vetting it with various stakeholders, and performing a field test that evaluates feasibility, reliability, and validity.
      ii. Domains include effectiveness of care, access of care, experience of care, utilization and relative resource use, and health plan descriptive information.
   b. The Quality Compass is a comparison tool that allows users to view measure results and benchmark information that ranks health plans using the HEDIS measures.
D. The National Quality Forum is a nonprofit organization that aims to improve quality through a three-part mission. (1) Build consensus on national priorities and goals for performance improvement and work in partnership to achieve them. (2) Endorse national consensus standards for measuring and publicly reporting on performance. (3) Promote the attainment of national goals through education and outreach programs.

1. Membership includes stakeholders from consumer organizations, public and private purchasers, physicians, nurses, accrediting and certifying bodies, supporting industries, and health care research and quality improvement organizations.

2. Through the passage of the Medicare Improvements for Patients and Providers Act of 2008, the DHHS entered into a contract with the National Quality Forum 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.
   a. Formulation of a national strategy and priorities for health care performance measurement to review and synthesize evidence related to 20 high-priority conditions identified by CMS that account for more than 95% of their costs
   b. Implementation of a consensus process for endorsement of health care quality measures
   c. Maintenance of consensus-endorsed measures
   d. Promotion of EHRs
   e. Focused measurement of the development, harmonization, and endorsement efforts to fill critical gaps in performance measurements

E. The Agency for Healthcare Research and Quality (AHRQ)

1. Basics
   a. The agency within the DHHS that supports research that helps people make more 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.

2. Definitions
   a. Comparative Effectiveness Research (CER) is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. The concept of CER was introduced in the Medicare Modernization Act of 2003, but it received more funding and attention in ARRA 2009 when the Federal Coordinating Council for Comparative Effectiveness was established. It is composed of members from DHHS agencies such as the AHRQ, FDA, NIH, CMS, CDC, Office of Minority Health, Office of the National Coordinator, Health Resources and Services Administration, and Substance Abuse and Mental Health Services as well as from the Veterans Health Administration and the Department of Defense and Office of Management and Budget.
   b. The Consumer Assessment of Healthcare Providers and Systems assesses consumer experiences with health care. The Clinician and Group, Health Plan, and In-Center Hemodialysis surveys can be reviewed by patients and consumers, quality monitors and regulators, provider organizations, health plans, community collaboratives, and public and private purchasers of health care as a means to make informed decisions and improve health care services.
   c. The Effective Health Care Program funds individual researchers, research centers, and academic organizations to work together with AHRQ to produce effectiveness and CER for clinicians, consumers, and policy-makers.
d. According to the Institute of Medicine (IOM), health service research is a multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of health care services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations.

F. The Pharmacy Quality Alliance
   1. Basics
      a. The mission of the Pharmacy Quality Alliance is to improve the quality of medication use across health care settings through a collaborative process in which key stakeholders agree on a strategy for measuring and reporting performance information related to medications.
      b. Develops 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
   2. Demonstration projects have been funded across the country.

VII. INSTITUTIONAL MEDICATION USE POLICY CONSIDERATIONS

A. Basics
   1. Formulary management
      a. The Joint Commission Medication Management Standard 02.01.01 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.
      b. The CMS CoP requires that medical staff establish a formulary system.
      c. An ongoing process for a health care organization to establish medication use policies on drugs, therapies, and drug-related products that are evidence based and cost-effective for certain patient populations
      d. A 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. This process is used to assess the appropriateness of drug therapy by evaluating data on drug use in a given health care environment compared with predetermined criteria and standards (Table 8).

Table 8. Elements of a Drug Use Evaluation Monograph

| • Brand and nonproprietary names | • Pregnancy category and use in breastfeeding mothers |
| • FDA approval information, including date and FDA rating (see III.D.4.d and e) | • Clinical trial analysis and critique |
| • For biosimilars, interchangeability status | • Comparison of efficacy, safety, and cost-effectiveness |
| • Pharmacology and mechanism of action | • Medication safety assessment and considerations |
| • FDA-approved indications | • Financial analysis based on use within a health system |
| • Potential off-label uses | • Recommendation for inclusion or exclusion |
| • Dosage forms and strengths | • Use in special populations (e.g., pediatric, geriatric, hepatic, or renal insufficiency) |
f. Formulary management strategies
   i. Preferential use of generic drugs
   ii. Formulary exclusions
   iii. Formulary restrictions: Restricting prescriptive authority to a particular service or disease state
   iv. Therapeutic interchange: Authorized exchange of therapeutic alternatives in accordance with previously established and approved written guidelines, policies, or protocols within a formulary system
   v. Guided-use requirements: Include use criteria, clinical practice guidelines, and operating procedures

2. Medication safety
   a. Medication errors are the broadest category and have the highest frequency of occurrence, whereas adverse drug events are rare, occurring in 1% of medication errors.
      i. There are grades of certainty criteria, including certainty, probable/likely, possible, and unlikely, to determine whether an adverse event is caused by a medication.
      ii. Table 9 outlines the differences between medication errors, adverse drug events, and adverse drug reactions, or nonpreventable adverse drug events.

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

b. 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 titled “Patient Safety: Achieving a New Standard for Care” revealed the high incidence of adverse events occurring in hospitals.

c. The Patient Safety and Quality Improvement Act of 2005 (Patient Safety Act) and the Patient Safety and Quality Improvement Final Rule (Patient Safety Rule) were a congressional response to these reports.
      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) PSOs can be 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.
         (c) 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.
iii. 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 nonidentifiable.

iv. 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.

(a) 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.

(b) CMS surveyors were also encouraged to become familiar with Common Formats.

d. Adverse drug events should be reported to the FDA Adverse Event Reporting System, a database with more than 400 million adverse event and medication error reports.

i. MedWatch Form FDA 3500 for voluntary reporting is for health care professionals to report a serious adverse event, product quality problem, or product use error with an FDA-regulated drug, biologic, medical device, or dietary supplement. 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 IND and biologic regulations and user facilities such as hospitals and nursing homes.

iii. MedWatch Form FDA 3500B is available for consumer reporting.

iv. Vaccine-related adverse effects, veterinary medicine product adverse events, and suspected unlawful Internet sales of medical products should not be reported to MedWatch.

v. The Sentinel Initiative 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.

e. The Institute for Safe Medication Practices began in 1975 to promote medication error prevention and initiated a voluntary practitioner error-reporting program.

i. The institute is a nonprofit PSO.

ii. Publishes four medication safety alert newsletters for acute care settings, ambulatory care settings, nurses, and medications.

f. The University HealthSystem Consortium (UHC) is an alliance of academic medical centers and affiliated hospitals.

i. Is an AHRQ-listed PSO: The UHC Performance Improvement PSO.

ii. 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.

3. Compounding implications

a. The USP develops standards, enforceable by the FDA, on the identity, strength, quality, and purity of medications and dietary supplements, including compounded products.

b. The General Chapters can be required (numbered below <1000>), informational (numbered<1XXX), or 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: Pharmaceutical Compounding for Sterile Preparations

iii. USP 800 (in progress): Hazardous Drugs: Handling in Healthcare Settings
c. Pharmacies may be subject to inspection against these standards by boards of pharmacy, the FDA, the Joint Commission, and other entities.

d. USP 797 standards assign risk levels (low, medium, and high) according to requirements for the types of admixtures and preparation procedures.

e. CSPs have been under scrutiny because of deaths associated with microorganism contamination. 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 according to the level of risk and storage (Table 10).

**Table 10. Beyond-Use Dating for Compounded Sterile Products**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Room Temperature</th>
<th>Refrigerator</th>
<th>Freezer (≤–10°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate use</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Low w/12-hr beyond-use date</td>
<td>12 hours or less</td>
<td>12 hours or less</td>
<td>N/A</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>

**B. Definitions**

1. A *formulary* is a continually updated list of medications and related information, representing the clinical judgment of pharmacists, physicians, and other experts in the diagnosis and treatment of disease and promotion of health.

2. An *adverse drug event* is an injury resulting from medication use, including physical harm, mental harm, or loss of function.

3. An *adverse drug reaction*, a nonpreventable adverse drug event, is a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function.

4. A *medication error* is any error occurring in the medication process (ordering, transcribing, dispensing, administering, and monitoring).

5. Common formats refers to the common definitions and reporting formats that allow health care providers to collect and submit standardized information about patient safety events.

6. A *compounded sterile product* is a biologic, diagnostic, drug, nutrient, or radiopharmaceutical that is prepared according to the manufacturer’s labeled instructions and other manipulations that expose its contents to potential contamination or that contains nonsterile ingredients or uses nonsterile components or devices that must be sterilized before administration.
REFERENCES

Congressional Offices with Jurisdiction over Health-Related Policy and the Legislative Process


Agencies of DHHS with Primary Regulatory Impact on the Practice of Pharmacy


The FDA and the Prescription Drug Approval Process


IRB Implications for Clinical Practice and Research

Investigational Drug Services


The Joint Commission, National Committee for Quality Assurance, National Quality Forum, and Agency for Healthcare Research and Quality


ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **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 mandatory form to be submitted by IND reporters, manufacturers, distributors, importers, and facility personnel. Manufacturers, packers, and distributors should not include the names and addresses of individual patients. However, health care providers can 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.

2. **Answer: B**
A generic drug must prove bioequivalence to a branded product to gain approval. The regulatory pathway for a generic drug is through the ANDA, not through the Accelerated New Drug Application. Generic drugs need not be therapeutically equivalent to a branded product; however, if they are not therapeutically equivalent, they will be rated “B” in the Orange Book.

3. **Answer: A**
If a drug is subject to an ETASU REMS that requires the provision and review of a medication guide, it must be provided in all settings as specified in the REMS program. Requirements of an REMS to provide a medication guide can be revised and removed after approval at a later point.

4. **Answer: B**
An IND application 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. 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.

5. **Answer: C**
Answer A matches a phase I trial, Answer B matches a phase III trial, and Answer D matches a phase IV trial.

6. **Answer: D**
Title 45 CFR Part 46 pertains to the protection of human subjects. The Belmont Report served as a foundation for the guiding principles of ethics in human subjects research. The DHHS and the FDA used this report to revise their existing human subjects regulations, and a decade later the Federal Policy for the Protection of Human Subjects, or the “Common Rule,” was published. Part 46 is divided into the following subparts:
(A) the basic DHHS Policy for Protection of Human Research Subjects; (B) additional protections for pregnant women, human fetuses, and neonates involved in research; (C) additional protections pertaining to biomedical and behavioral research involving prisoners as subjects; (D) additional protections for children involved as subjects in research; and (E) the registration of IRBs. The HIPAA Privacy Rule is listed in Title 45, Public Welfare, as well as in the Common Rule; however, it
is in a different part of the latter. Bioavailability and bioequivalence requirements are listed in Title 21, Food and Drugs. Finally, the Vaccine Injury Compensation Program is listed in Title 42, Public Health.

7. **Answer: A**
An adverse drug reaction is a nonpreventable adverse drug event that is not the result of a medication error. Answer B is the definition of an adverse drug event, Answer C is the definition of a preventable adverse drug event, and Answer D is the definition of a potential adverse drug event.

8. **Answer: D**
Compounded sterile products, independent of risk level, can be stored for a maximum of 45 days in the freezer. The beyond-use dating differs according to risk level (low, medium, or high) if stored at room temperature or in a freezer. If a CSP has undergone sterility testing, however, it can be assigned a beyond-use date according to the maximum chemical stability permitted by valid references.

9. **Answer: B**
The Drug Price Competition and Patent Term Restoration Act of 1984 is commonly called the Hatch-Waxman Act, named after the two lead sponsors, Representative Henry Waxman and Senator Orrin Hatch. The Kefauver-Harris Amendments pertain to the requirement of a drug to show efficacy in addition to safety. The Durham-Humphrey Amendment differentiated prescription drugs from nonprescription drugs. The Biologics Price Competition and Innovation Act of 2009 was a provision passed in the 2010 ACA, and it created an abbreviated approval pathway for follow-on biologic products, or biosimilars.