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Pharmacology

A Patient-Centered Nursing Process Approach

EDITION 9

ELSEVIER

Pharmacology

A Patient-Centered Nursing Process Approach

NINTH EDITION

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3251 Riverport Lane
St. Louis, Missouri 63043

PHARMACOLOGY: A PATIENT-CENTERED NURSING PROCESS APPROACH ISBN: 978-0-323-39916-6
NINTH EDITION

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Library of Congress Cataloging-in-Publication Data
Names: McCuistion, Linda E., author. | Vuljoin-DiMaggio, Kathleen, author.
|

Winton, Mary B., author | Yeager, Jennifer J., author. | Preceded by (work): Kee, Joyce LeFever. Pharmacology.
Title: Pharmacology : a patient-centered nursing process approach / Linda McCuistion, Kathleen Vuljoin-DiMaggio, Mary B. Winton, Jennifer J. Yeager.
Description: 9th edition. | St. Louis, Missouri : Elsevier, [2018] | Preceded by Pharmacology / Joyce LeFever Kee, Evelyn R. Hayes, Linda E. McCuistion.
8th edition. 2015. | Includes bibliographical references and index.
Identifiers: LCCN 2016052177 | ISBN 9780323399166 (pbk. : alk. paper)
Subjects: | MESH: Pharmacological Phenomena | Pharmaceutical Preparations | Drug Therapy | Patient-Centered Care | Nurses' Instruction
Classification: LCC RM301 | NLM QV 4 | DDC 615.5/8--dc23 LC record available at https://lccn.loc.gov/2016052177

Executive Content Strategist: Sonya Seigafuse
Content Development Manager: Lisa Newton
Senior Content Development Specialist: Tina Kaemmerer
Publishing Services Manager: Jeff Patterson
Senior Project Manager: Tracey Schriefer
Design Direction: Maggie Reid

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Dedication

To Dr. Gerald DeLuca for his expert guidance; to Joyce LeFever Kee, who originated this book; to Evelyn R. Hayes for her efforts; and in memory of my parents, Otto and Pauline Schmidt.

Linda E. McCuistion

To Dr. Linda McCuistion, for her friendship and guidance, and to my daughters, Christina Boudreaux, Maria DiMaggio, and Katie Leboutillier for their constant love and encouragement.

Kathleen Vuljoin-DiMaggio

To my Lord and Savior for the gift of nursing and teaching, to Dr. Richard A. Winton for his love and support for many years, and in loving memory of my parents, Matthew and Mary Wagner.

Mary B. Winton

To Tracy L. Yeager, my husband, my rock, and support; and to my boys, Jacob and Joshua, for just being boys.

Jennifer J. Yeager

Meet the Authors

Linda E. McCuistion

Dr. Linda E. McCuistion received a Diploma of Nursing from the Lutheran Hospital School of

Nursing in Fort Wayne, Indiana; Bachelor of Science in Nursing from William Carey College in Hattiesburg, Mississippi; Masters in Nursing from Louisiana State University Medical Center, New Orleans; and PhD in Curriculum and Instruction from the University of New Orleans. She was licensed as an Advanced Practice Nurse in Louisiana and has many years of nursing experience that include acute care and home health nursing. For 20 years, Linda was a Nursing Professor at Our Lady of Holy Cross College in New Orleans, Louisiana. She received an Endowed Professorship Award in 2000 and 2003. Linda worked as a nursing professor at South University, Richmond, Virginia, for 3 years. Currently, Linda teaches NCLEX® review courses for Elsevier.

Linda has served as a past president, vice president, and faculty advisor of the Sigma Theta Tau International Honor Society in Nursing, Xi Psi chapter-at-large. She is a past associate editor of the *NODNA Times,* a New Orleans District Nurses Association newsletter. She has been a member of Phi Delta Kappa and the American Society of Hypertension.

Linda was coordinator for the Graduate Plus internship program, a preceptorship program for new nursing graduates in the state of Louisiana. She has served as a legal nurse consultant; a member of a medical review panel; advisory board member, consultant, and reviewer of a software preparation company focused on the state licensure examination; advisory board member for a school for surgical technicians; and consultant to a local hospital to improve the quality of nursing care and assist acute care facilities in preparation for accreditation.

Linda was chosen as a "Great One-Hundred Nurse" by the New Orleans District Nurses Association in 1993. She is also listed in the 2005/2006 edition of the Empire Who's Who Executive and Professional Registry.

Linda has given numerous lectures and presentations regionally and nationally on a variety of nursing topics. She has published articles in nursing journals and has authored many chapters in several nursing textbooks, including *Pharmacotherapeutics: Clinical Decision Making in Nursing* (1999), *Saunders Manual of Medical-Surgical Nursing: A Guide for Clinical Decision Making* (2002), and *Saunders Nursing Survival Guide: Pathophysiology* (2007). She is author and coauthor of many chapters and coeditor of *Saunders Nursing Survival Guide: Pharmacology* (2007).

Linda enjoys cruises and other travel. When at home, she enjoys family, friends, golf, crafts, playing bridge, and writing.

Kathleen Vuljoin-DiMaggio

Kathleen Vuljoin-DiMaggio received her Bachelor of Science in Nursing from Our Lady of Holy Cross College of New Orleans and her Master of Science in Nursing from Loyola University of New Orleans, with a focus on Healthcare Systems Management. She completed a preceptorship in palliative care at Ochsner Foundation Hospital through Loyola University. She received Level I designation from the National Hospice and Palliative Care Organization in hospice management and development. She is certified with the Louisiana Department of Health and Hospitals Developmental Disabilities as a Registered Nurse Instructor in medication administration. Kathleen has over 20 years of clinical nursing experience and over 9 years of baccalaureate nursing education. Her professional practice experience includes medical-surgical nursing, neurologic nursing, and home health and hospice nursing. She has experience in nursing management and has worked as director of nursing for a facility specializing in developmental disabilities. In addition, Kathleen has worked as director of nursing in home health and hospice care. She has worked in quality improvement, disease management, and case management.

Kathleen teaches medical-surgical nursing at both junior and senior levels. She teaches in Perspectives of Nursing, a senior launching course, and serves as coordinator of Professional Dimensions of Nursing. She is an academic nursing advisor and serves on the Curriculum Committee, Administrative Council Committee, and Diversity Committee.

Kathleen has served as a volunteer for Junior Achievement of New Orleans, has volunteered for a local hospice agency, and has served in the homeless ministry through her church.

Kathleen is a member of the American Nurses Association, Louisiana State Nurses Association, and Sigma Theta Tau International Honor Society of Nursing, and she is a member of the Alpha Sigma Nu Jesuit Honor Society.

Kathleen is a recipient of the 2011 and 2015 Endowed Professorship from Eminent Eye, Ear, Nose and Throat Hospital. She has received the Order of St. Louis Award through the Archdiocese of New Orleans and has also received the Florence Nightingale Society Award for Nursing.

Kathleen enjoys time with her friends, daughters, and grandchildren. She enjoys golfing, quilting, and cooking.

Dr. Mary B. Winton received her Associate Degree in Nursing from Tarleton State University in Stephenville, Texas, a member of the Texas A&M University System; her Bachelor and Master of Science in Nursing from the University of Texas at Arlington; and her PhD in Nursing from the University of Texas at Tyler. Additionally, she is board certified through the American Nurses Credentialing Center as an Acute Care Adult Nurse Practitioner. Mary has many years of hospital nursing experience that include critical care and nursing supervisor. Additionally, she was employed with a hospitalist group as an Acute Care Nurse Practitioner for many years. She is currently an Assistant Professor in the College of Health Sciences and Human Services, Department of Nursing, at Tarleton State University. Mary has experience in teaching graduate-level pharmacology and pathophysiology and nursing informatics and has vast experience teaching at all levels of the undergraduate nursing program, including nursing pathophysiology and pharmacology.

Mary has served as faculty advisor for the Student Nurses Association at Tarleton. She is a member of several organizations, including Sigma Theta Tau International Honor Society in Nursing, Tau Chi chapter; American Nurses Association/Texas Nurses Association; and Rural Nurse Organization. She is actively involved in various university, college, and departmental committees.

During her career as a nurse educator, Mary was the recipient of the Texas A&M Student Evaluation Teaching Excellence Award and the O.A. Grant Excellence in Teaching Award. She is involved in teaching English as a Second Language at her church of membership.

Mary's research interests include health disparity among minorities, especially among Korean immigrants; student learning outcomes; and the use of technology in classrooms. She has presented at several conferences and has published on the health care of Korean immigrants.

During her spare time, Mary enjoys spending time with her husband, daughters, and grandchildren. She also enjoys traveling, reading, crocheting, and snow skiing.

Jennifer J. Yeager

Dr. Jennifer J. Yeager graduated from the University of Portland, Oregon, in 1987 with her Bachelor of Science in Nursing degree; she attended the university on an Air Force ROTC nursing scholarship. Following graduation, she began her nursing career as an Air Force officer, assigned to Wilford Hall USAF Medical Center in San Antonio, Texas. The Air Force provided Jennifer with excellent experience as a transplant/nephrology nurse, and after 6 years of active duty she entered the civilian world as a transplant coordinator at Methodist Medical Center in Dallas, Texas. While there, Jennifer began her Master of Science in Nursing degree at the University of Texas at Arlington, and she completed her degree as an Adult/Gerontological Nurse Practitioner with

Educator Role in 1998. After completing ANCC certification in both specialty areas, she went to work in the Baylor Health Care System as a nurse practitioner in Long-term Care and Elder House Calls.

Jennifer moved to Stephenville, Texas, in 2007 and began teaching at Tarleton State University, where she is now Director of the Graduate Nursing Program and RN-BSN Liaison. Since then, she has taught nursing care of the older adult, pharmacology, and research to undergraduate students and RN-BSN students as well as teaching nursing theory, informatics, teaching methods and strategies, pharmacology, and assessment at the master's level. She completed her PhD in Nursing at the University of Texas at Tyler in fall 2013. The findings from her dissertation research were presented at the National Gerontological Nursing Association's annual convention in San Antonio, Texas, in 2014. Currently, she is project director on a research grant funded through the Texas Higher Education Coordinating Board, Nursing Innovation Grant Program, titled "Enhancing Simulation Realism and Building Lab and Simulation Capacity in a Rural BSN Program." Along with a coworker, Jennifer presented the findings from a previous simulation grant at the International Meeting on Simulation in Health Care in San Diego, California, in 2016.

Jennifer currently serves as President of the Tau Chi chapter of Sigma Theta Tau International and as Book Salon Chair for the Society for Simulation in Health Care. She has been involved with revising and reviewing Lehne's *Pharmacology for Nursing Care,* including online components and the study guide, since 2007. She revised chapters for the fifth edition of Meiner's *Gerontologic Nursing.*

To relax, Jennifer enjoys spending time with her family, including multiple dogs. She is a strong advocate for dog rescue organizations and is a member of Pets Are Worth Saving in Stephenville, Texas. Additionally, she enjoys reading, food, and watching television.

In Recognition

Joyce LeFever Kee taught a pharmacology course to student nurses for 10 years from 1980 to 1990 at the University of Delaware. At the time, there were very few pharmacology texts available and what was published was not appropriate for some BSN and ADN nursing programs. Daniel Ruth from W.B. Saunders approached Kee in 1990 to write a pharmacology book for nurses. With experience in teaching the subject, Kee developed the contents and format for a pharmacology text.

The chapter, Drug Action: Pharmaceutic, Pharmacokinetics, and Pharmacodynamics phases, became the first chapter. These drug phases appear both in the Prototype Drug Charts and within the contents in most of the current chapters. There are many drug tables Kee developed which have been updated by co-authors through the years. The important part that Kee established in the chapters were the five steps of the Nursing Process.

Dr. Evelyn R. Hayes joined Kee starting with the first edition. Hayes developed certain chapters and took the responsibility to work with contributors for the book such as the six chapters on Reproductive and Gender-Related Agents among others.

Linda McCuistion joined Kee and Hayes in 2005. McCuistion has updated many of Kee's chapters with new drugs and content.

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Preface

The ninth edition of *Pharmacology: A Patient-Centered Nursing Process Approach* is written for nursing students who can benefit from presentation of the principles of pharmacology in a straightforward, student-friendly manner. It focuses on need-to-know content and helps students learn to administer drugs safely and eliminate medication errors through extensive practice of dosage calculations and evidence-based application of the nursing process.

Organization

Pharmacology: A Patient-Centered Nursing Process Approach is organized into 18 units and 55 chapters. **Unit I** is an introduction to pharmacology and includes thoroughly updated chapters on drug action, the drug approval process, cultural and pharmacogenetic considerations, drug interactions, over-the-counter drugs, drugs for substance use disorder, complementary and alternative therapies, lifespan issues, patient collaboration in community settings, and the role of the nurse in drug research.

Unit II focuses on patient care and safety, with completely revised and updated chapters on the nursing process in patient-centered pharmacotherapy, safety and quality in pharmacotherapy, and medication administration. **Unit II** features an introduction to the Quality and Safety Education for Nurses (QSEN) initiative, with special emphasis on patient-centered care and on the QSEN competencies of safety and quality. **Unit II** also features a comprehensive review of drug dosage calculations for adults and children and is a unique strength of this book. This unit, tabbed for quick reference, consists of five sections: Systems of Measurement with Conversion Factors, Calculation Methods: Enteral and Parenteral Drug Dosages, Calculation Methods: Drugs That Require Reconstitution, Calculation Methods: Insulin Dosages, and Calculation Methods: Intravenous Flow Rates. Five methods of dosage calculation are presented, with color coding for easy identification: basic formula, ratio and proportion/fractional equation, dimensional analysis, body weight, and body surface area. Integral to the sections on dosage calculations are clinical practice problems that feature actual drug labels in full color, which provides extensive practice in real-world dosage calculations. With this wide array of practice problems in a variety of health care settings, this unit eliminates the need to purchase a separate dosage calculations book.

Unit III addresses nutrition, fluids, and electrolytes with separate chapters that cover vitamin and mineral replacement, fluid and electrolyte replacement, and nutritional support.

Units IV through XVIII make up the core of *Pharmacology: A Patient-Centered Nursing Process Approach* and covers the drug classifications that students must understand to practice effectively. Each drug family chapter includes a chapter outline, learning objectives, key terms, at least one prototype drug chart, a drug table, and an extensive nursing process section.

- The **prototype drug charts** are a unique tool that students can use to view the many facets of a prototype drug through the lens of the nursing process. Each prototype drug is one of the common drugs in its drug class. The charts include drug class, contraindications, dosage, drug-lab-food interactions, pharmacokinetics, pharmacodynamics, therapeutic effects/uses, side effects, and adverse reactions. With these charts, students can see how the steps of the nursing process correlate with these key aspects of drug information and therapy.
- The **drug tables** provide a quick reference to routes, dosages, uses, and key considerations for the most commonly prescribed medications for a given class. They list the drug's generic names, dosages, uses and considerations, pregnancy categories, and specific information on half-life and protein binding.
- The **nursing process sections** provide a convenient summary of patient assessments, potential nursing diagnoses, plan of care, and outcomes. These sections also include cultural content, nursing interventions, suggestions for patient teaching, and relevant herbal information.

Additional Features

Throughout this edition, we have retained, enhanced, and added a variety of features that teach students the fundamental principles of pharmacology and the role of the nurse in drug therapy:

- **NCLEX study questions** at the end of each chapter help prepare students for the NCLEX examination with its increasing emphasis on pharmacology; answers are listed upside down below the questions for quick feedback.
- **Patient safety boxes** include information on medication safety, complementary and alternative therapies, and more.
- **Key terms** include page numbers and are defined in the text to enhance this "built-in glossary" feature for students.
- **Critical thinking case studies** conclude most chapters. These clinical scenarios are followed by a series of questions that challenge students to carefully consider the scenario and apply their knowledge and analytical skills to respond to the situations.
- **Complementary and alternative therapies** appear throughout the text to provide students with a quick reference to information on popular herbs and their side effects, drug interactions, and more.
- **Anatomy and physiology** unit openers for all drug therapy chapters include illustrated overviews of normal anatomy and physiology. These introductions give students the foundation for understanding how drugs work in various body systems.
- **High-alert drugs** (denoted with the symbol) and **safety concerns** (denoted with the symbol) are identified within the text with distinctive icons that make it easy to find crucial information.

Teaching and Learning Resources

The ninth edition of *Pharmacology: A Patient-Centered Nursing Process Approach* is the core of a complete teaching and learning package for nursing pharmacology. Additional components of this package include resources for students, resources for faculty members, and resources for both students and faculty.

For Students

A comprehensive *Study Guide,* available for purchase separately, provides thousands of study questions and answers, including clinically based situational practice problems, drug calculation problems and questions (many with actual drug labels), and case studies to help students master textbook content. Answers are provided at the end of the *Study Guide*.

A completely updated Evolve website (http://evolve.elsevier.com/McCuistion/pharmacology) provides additional resources for students, including the following:

- **Review questions for the NCLEX® Examination** organized by chapter
- **Downloadable key points** for content review on the go
- **Pharmacology animations** and **videos**
- **Unfolding case studies** with review questions

For Faculty Members

The updated faculty Evolve website (http://evolve.elsevier.com/McCuistion/pharmacology) includes all of the student resources mentioned previously plus the following instructor-only resources:

- ***TEACH for Nurses* lesson plans** focus on the most important content from each chapter and provide innovative strategies for student engagement and learning. The lesson plans include strategies for integrating nursing curriculum standards (QSEN, concept-based learning, and BSN essentials), links to all relevant student and instructor resources, and an original instructor-only case study in each chapter.
- **ExamView Test Bank** features more than 1000 NCLEX® Examination–format questions that include alternate-item questions as well as rationales and page references for each question.
- **PowerPoint Collection** features customizable slides with images, integrated audience response system questions, and new unfolding case studies with questions.

• **Image Collection** provides approximately 125 full-color images from the book.

This textbook may be supplemented with the drug content found on government agency websites, which supply the latest information regarding changes to drug brand names.

It is our hope that *Pharmacology: A Patient-Centered Nursing Process Approach* and its comprehensive ancillary package will serve as a dynamic resource for teaching students the basic principles of pharmacology and their vital role in drug therapy.

Linda E. McCuistion

Kathleen Vuljoin-DiMaggio

Mary B. Winton

Jennifer J. Yeager

Acknowledgments

We wish to extend our sincere appreciation to the many professionals who assisted in the preparation of the ninth edition of *Pharmacology: A Patient-Centered Nursing Process Approach* by reviewing chapters and offering suggestions.

We wish to especially thank Joyce LeFever Kee, who originated this pharmacology textbook, and her coauthor Evelyn R. Hayes, who worked tirelessly on many editions of this book.

We wish to thank the current contributors: Christina DiMaggio Boudreaux, Bettyrae Jordan, Linda Laskowski-Jones, Suzanne Riche, and Jared Robertson.

We wish to thank those who created and updated the previous established chapters: Margaret Barton-Burke, Joseph Boullata, Jacqueline Rosenjack Burchum, Katherine L. Byar, Michelle M. Byrne, Karen Carmody, Robin Webb Corbett, Sandy Elliott, Linda Goodwin, Janice Heinssen, Marilyn Herbert-Ashton, Judith W. Herrman, Kathleen J. Jones, Bettyrae Jordan, Robert J. Kizior, Paula R. Klemm, Anne E. Lara, Linda Laskowski-Jones, Ronald J. LeFever, Patricia S. Lincoln, Patricia O'Brien, Laura K. Williford Owens, Byron Peters, Lisa Ann Plowfield, Larry D. Purnell, Nancy C. Sharts-Hopko, Jane Purnell Taylor, Donald L. Taylor, Lynette M. Wachholz, Marcia Welsh, Gail Wilkes, and M. Linda Workman.

Of course, we are deeply indebted to the many patients and students we have had throughout our many years of professional nursing practice. From them we have learned many fine points about the role of therapeutic pharmacology in nursing practice.

Our deepest appreciation goes to pharmaceutical companies for use of their drug labels. Pharmaceutical companies that extended their courtesy to this book include the following:

- Abbott Laboratories
- AstraZeneca Pharmaceuticals
- Aventis
- Bayer Corporation
- Bristol-Myers Squibb (including Apothecon Laboratories and Mead Johnson Pharmaceuticals)
- DuPont/Merck Pharmaceuticals
- Eli Lilly and Company
- Elkins-Sinn, Inc.
- Glaxo-Wellcome
- Marion Merrell Dow, Inc.
- McNeill Laboratory, Inc.
- Merck and Co., Inc.
- Parke-Davis Co.
- Pfizer Inc.
- Rhone-Poulenc Rorer
- SmithKline Beecham Pharmaceutical
- Wyeth-Ayerst Laboratories

Thanks to Becton, Dickinson and Company for the syringe displays. Thanks to CareFusion Corporation for the photos of the infusion pumps.

Our sincere thanks to Elsevier, especially Jamie Blum and Sonya Seigafuse, Content Strategists; Tina Kaemmerer, Senior Content Development Specialist; Tracey Schriefer, Senior Project Manager–Book Production; and Charlene Ketchum, Freelance Content Development Specialist, for their suggestions and assistance.

Linda E. McCuistion

Kathleen Vuljoin-DiMaggio

UNIT I
Introduction to Pharmacology

OUTLINE

Introduction

When administering drug therapy, it is important that nurses have an understanding of the drug development process and their responsibilities related to drug development and ethical research practices. These topics are discussed in Chapter 1, Drug Development and Ethical Considerations.

Assessing a patient's response to drug therapy is an ongoing nursing responsibility. To adequately assess, plan, intervene, and evaluate drug effects, the nurse must have knowledge of the pharmacokinetic and pharmacodynamic phases of drug action as well as current advances in pharmacogenetics, which are described in Chapter 2, Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics.

Chapter 3, Cultural Considerations, helps the nurse understand and respond to unique cultural factors that may influence adherence to drug therapy for a particular patient. Factors such as heritage, communication styles, family organization, spirituality and religion, health beliefs and practices, and traditional medicine are discussed.

Chapter 4, Complementary and Alternative Therapies, explores herbal supplements that are available over the counter. It covers the most commonly used herbs and discusses their indications, potential hazards, and tips for safe and effective use.

Chapter 5, Pediatric Considerations, and Chapter 6, Geriatric Considerations, cover pharmacokinetic and pharmacodynamic effects specific to these age groups. They also discuss the special attention required when administering drugs to these age groups.

Whereas most drugs are used safely and within prescribed guidelines, it is possible for all drugs to be misused. Drugs that are misused cause serious and complex social and health issues with negative consequences for both the individual and society. This is the topic of Chapter 7, Drugs in Substance Use Disorder.

Drug Development and Ethical Considerations

OUTLINE

OBJECTIVES

- Identify the three core ethical principles.
- Relate the core ethical principles that govern informed consent and risk-benefit ratio.
- Discuss the 2015 American Nurses Association Code of Ethics and its nine provisions.
- Describe the objectives of each phase of human clinical experimentation.
- Discuss federal legislation acts related to U.S. Food and Drug Administration drug approvals.
- Explain the Canadian schedules for drugs sold in Canada.
- Describe the function of state nurse practice acts.
- Differentiate between chemical, generic, and brand names of drugs.
- Define "over the counter" as it relates to drugs.
- Identify three useful drug reference resources.

KEY TERMS

American Nurses Association (ANA) Code of Ethics, p. 6
autonomy, p. 3
beneficence, p. 4
brand (trade) name, p. 11
chemical name, p. 11
controlled substances, p. 8
Critical Path Initiative, p. 2
dependent variable, p. 4
generic name, p. 11
genotoxicity, p. 4
Good Clinical Practice (GCP) Consolidated Guideline, p. 4
independent variable, p. 4
informed consent, p. 3
justice, p. 4
over-the-counter (OTC), p. 11
placebo, p. 6
respect for persons, p. 3
risk-benefit ratio, p. 4
U.S. Food and Drug Administration (FDA), p. 2

http://evolve.elsevier.com/McCuistion/pharmacology

Approval of new drugs by the **U.S. Food and Drug Administration (FDA)** has been steady since the early 2000s, reaching an all-time high in 2014 with the approval of 44 new drugs. To facilitate this increase, in 2004 the FDA established its **Critical Path Initiative**, a national strategy "to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured." One focus of this initiative is on "improving the prevention, diagnosis, and treatment of rare and neglected disorders." Initiative successes include developing biomarkers and other scientific tools, streamlining clinical trials, and ensuring product safety.

The process of drug discovery and manufacturing takes 10 to 12 years, with a cost of more than $1 billion for each drug. Out of every 5000 to 10,000 compounds that begin preclinical testing, only one makes it through the FDA approval process. The steps of the process are shown in Fig. 1.1. Drug research and development is a complex process that is of particular interest and importance to professional nursing practice.

This chapter is devoted to a description of basic ethical principles that govern drug development and the nurse's role in this process.

Core Ethical Principles

Three core ethical principles are relevant to research involving human subjects: **respect for persons**, beneficence, and justice. Derived from the Belmont Report, the World Medical Association Declaration of Helsinki set out ethical principles for medical research that involves human subjects. These ethical principles are integral to the issues of informed consent and risk-benefit ratio in such research.

Respect for Persons

Patients should be treated as independent persons who are capable of making decisions in their own best interests. Patients with diminished decision-making capacity are entitled to protection. When making health care decisions, patients should be made aware of alternatives available to them as well as the consequences that stem from those alternatives. The patient's choice should be honored whenever possible. It is imperative that nurses recognize when patients are not capable of making decisions in their own best interest and are therefore entitled to protection. The nurse can assist with the determination of decision-making capacity through frequent assessment of the patient's cognitive status.

Autonomy is an integral component of respect for persons. **Autonomy** is the right to self-determination. In health care settings, health care personnel must respect the patient's right to make decisions in their own best interest, even if the decision is not what the health care personnel want or think is best for the patient. Generally, patients can refuse any and all treatments (right of autonomy) except when the decision poses a threat to others—such as with tuberculosis, when taking medications is legally mandated. Autonomy is as relevant to the conduct of research as it is in health care decision making; Patients have the right to refuse to participate in a research study and may withdraw from studies at any time without penalty.

Informed Consent

Informed consent has its roots in the 1947 Nuremberg Code. The two most relevant aspects of the Code are the right to be informed and that participation is voluntary, without coercion. If coercion is suspected, the nurse is obligated to report this suspicion promptly. Informed consent has dimensions beyond protection of the individual patient's choice:

- It is a mutual sharing of information, a process of communication.
- It expresses respect for the person.
- It gains the patient's active involvement in their care.
- It respects the patient's right to self-determination.

It is the role of the health care provider, *not* the nurse, to explain the study and what is expected of the patient to the patient and to respond to questions from the patient. While giving written consent, the patient must be alert and able to comprehend; consent forms should be written at or below the eighth-grade reading level, and words should be kept to fewer than three syllables.

Nurses are patient advocates. In collaboration with the health care provider and the pharmacist, the nurse must be knowledgeable about all aspects of a drug study—including all inclusion and exclusion criteria for participants (Box 1.1), study protocol, and study-related documentation—in order to promote participant safety and quality study results.

Fig. 1.2 shows a sample of an informed consent form for a clinical drug trial, and Box 1.2 shows an informed consent checklist.

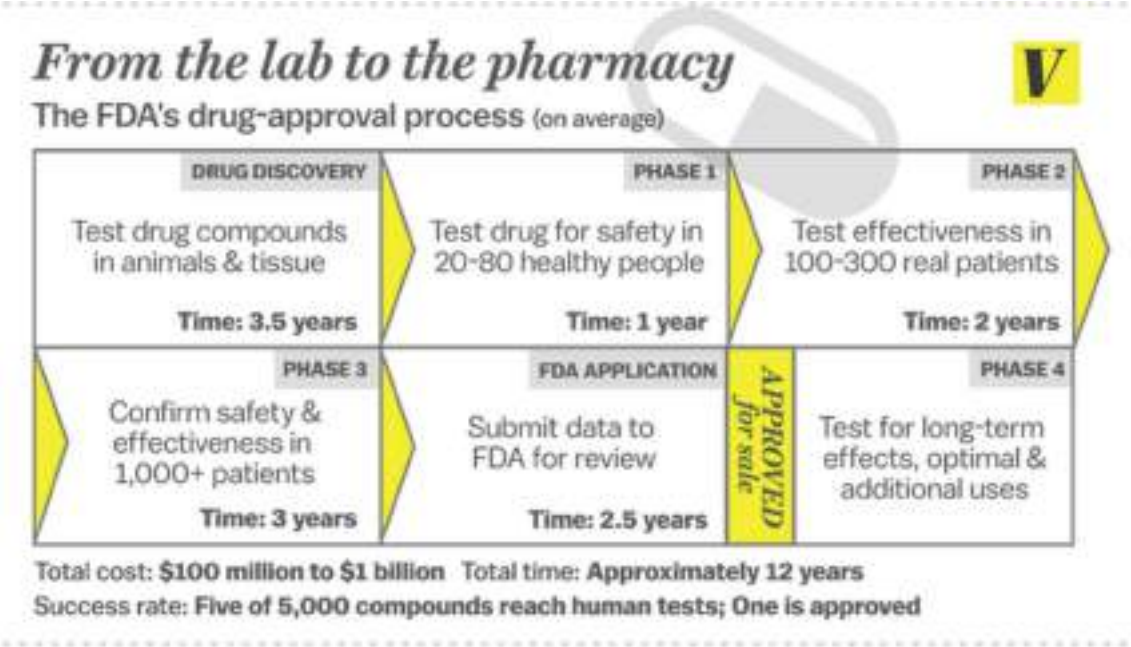


FIG. 1.1 The Drug Approval Process.

FDA, Food and Drug Administration. From Belluz, J. (2015). This new bill would add $9 billion for medical research. Here are 5 reasons critics are terrified. *VOX Science & Health.* Retrieved from http://www.vox.com/2015/7/14/8961923/21st-century-cures-act

BOX 1.1 Sample Inclusion and Exclusion Criteria

Inclusion

- Persons between the ages of 18 and 65
- Persons weighing between 50 and 100 kg
- Persons on a stable dose (i.e., no dose change in the previous 3 months) of cardiac medications (e.g., anticoagulants, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II–receptor blockers [ARBs], beta blockers, and diuretics)
- Persons adhering to a no-added-salt diet

Exclusion

- Women who are pregnant or nursing
- Women of childbearing age who do not use oral contraceptives
- Persons with symptomatic cardiac disease, hepatic dysfunction, chronic kidney disease, neurologic disorders, or musculoskeletal disorders
- Persons with clinically significant abnormal laboratory values (chemistry and hematology)

Beneficence

Beneficence is the duty to protect research subjects from harm. It involves assessing potential risks and possible benefits and ensuring the benefits are greater than the risk.

Risk-Benefit Ratio

The **risk-benefit ratio** is one of the most complex problems faced by the researcher. All possible consequences of a clinical study must be analyzed and balanced against the inherent risks and the anticipated benefits. Physical, psychological, and social risks must be identified and weighed against the benefits. A requirement of the Department of Health and Human Services (DHHS) is that institutional review boards (IRBs) determine that risks to subjects be reasonable in relation to the anticipated benefits, if any, for subjects. No matter how noble the intentions, the calculation of risks and benefits by the researcher cannot be totally accurate or comprehensive.

Justice

Justice requires that the selection of research subjects be fair. Research must be conducted so that the distribution of benefits and burdens is equitable (i.e., research subjects reflect all social classes and racial and ethnic groups).

Objectives and Phases of Pharmaceutical Research

The FDA requires clinical research to follow the **Good Clinical Practice (GCP) Consolidated Guideline**, an international ethical and scientific quality standard for designing, conducting, monitoring, auditing, recording, analyzing, and reporting clinical research. It is the foundation of clinical trials that involve human subjects. Additional guidance and information sheets are available from the FDA on multiple topics related to clinical research.

Preclinical Trials

Prior to the implementation of clinical research, the FDA requires preclinical trials to determine a drug's toxic and pharmacologic effects through in vitro and in vivo animal testing in the laboratory. Through these trials, drug developers are able to determine **genotoxicity**, the ability of a compound to damage genetic information in a cell, in addition to drug absorption, distribution, metabolism, and excretion.

Human Clinical Experimentation

Historically, drug research was done only with Caucasian males, causing uncertainty as to the validity of research results for people of other ethnicities and for women and children. In 1993, Congress passed the National Institutes of Health (NIH) Revitalization Act, which helped to establish guidelines to include women and minorities in clinical research. Additionally, the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003 encourage pharmaceutical companies to study their drugs in children.

Clinical experimentation in drug research and development encompasses four phases, each with its own objectives (see Fig. 1.1). A multidisciplinary team approach that includes nurses, physicians, pharmacologists, statisticians, and research associates is required to ensure safety and quality in all phases of clinical research. A brief description of each phase follows.

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II: The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

Phase III: The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV: Studies are done after the drug or treatment has been marketed to gather information on the drug's effects in various populations and to assess any side effects associated with long-term use.

Pharmaceutical companies are eager to bring new drugs to market. To reduce delays in the FDA approval process, in 1992 congress passed the Prescription Drug User Fee Act, which provided the FDA with funds to expedite the review process. As a result, the average drug approval time has decreased from 30 months to 12.

Clinical Research Study Design

An appropriate experimental design is important to answer questions about drug safety and efficacy. Studies are designed to determine the effect of the **independent variable** (treatment, such as with a drug) on the **dependent variable** (outcome, such as clinical effect). Intervening (extraneous) variables are factors that may interfere with study results, and these may include age, sex, weight, disease state, diet, and the subject's social environment. It is important to control for as many of the intervening variables as possible to increase study validity.

Sample Informed Consent Form for Randomized Clinical Trial of a Drug

Title of study: Comparison of a new drug [A] with an existing drug [B] used in treatment of disease X

Principal Investigator: Dr. ABC

Institute: Department of Pediatrics, Aga Khan University

Introduction:

I am Dr. [SAK] from Department of Pediatrics, the Aga Khan University and doing a research on treatment of disease [X, for example malaria]. There is a new drug [A] which is being recommended for its treatment. I want to see if the new drug [A] is as good as or better than the commonly used drug [B] for the treatment of disease [malaria]. Since you are a patient of (or suffering from) disease [malaria], I would like to invite you to join this research study.

Background information

Disease X (Malaria) is a common disease in Pakistan, Asia and Africa, caused by a germ (parasite) spread by mosquito. It causes high grade fever. Some patients may have complications and even die. The commonly used drugs are losing their effectiveness and germs are getting resistant to it. A new drug known as [A] is supposed to be effective in treatment of disease (malaria) but there is not enough evidence that it is as good as other drugs used for treatment of disease (malaria).

Purpose of this research study

The purpose of study is to find out if the new drug is as good as or better than other drugs used for treatment of malaria in our population and; also to see if germs are not resistant to it.

Procedures

In this study, all patients aged 15 to 50 years of age, presenting at the clinic with fever for less than one week duration and having no other diagnosis will be registered and screened for malaria. For diagnosis of disease (malaria), one ml of blood will be taken from the patients and checked for presence of germs (malarial parasite). Those patients having positive test for the disease (malaria), will be included in the study. They will be divided randomly in to two groups by a computer draw. One group will get the new drug (A) and the other group will get the commonly used drug (B). Neither the doctor nor the patient will know which drug he/she is getting for treatment of his/her disease. A record will be kept for the duration of fever and other symptoms including any other side effect. Other necessary treatment will also be provided if needed.

Possible risks or benefits

No significant side effects have been reported for this new drug (A). However, some patients may feel nausea or may have vomiting. Drawing of blood may cause some discomfort or blue discoloration at the site of bleeding. Lowering of white blood cells and platelet is a common feature of the disease.

There is no direct financial or other benefit for the participant of the study. However, all the investigations will be done free of cost to the patients and; the drugs (A) or (B) will be provided free. Treatment of any side effect will also be provided free of cost. Sponsor of the study will bear the cost of drugs, investigations and treatment of side effects related to the study drugs.

Right of refusal to participate and withdrawal

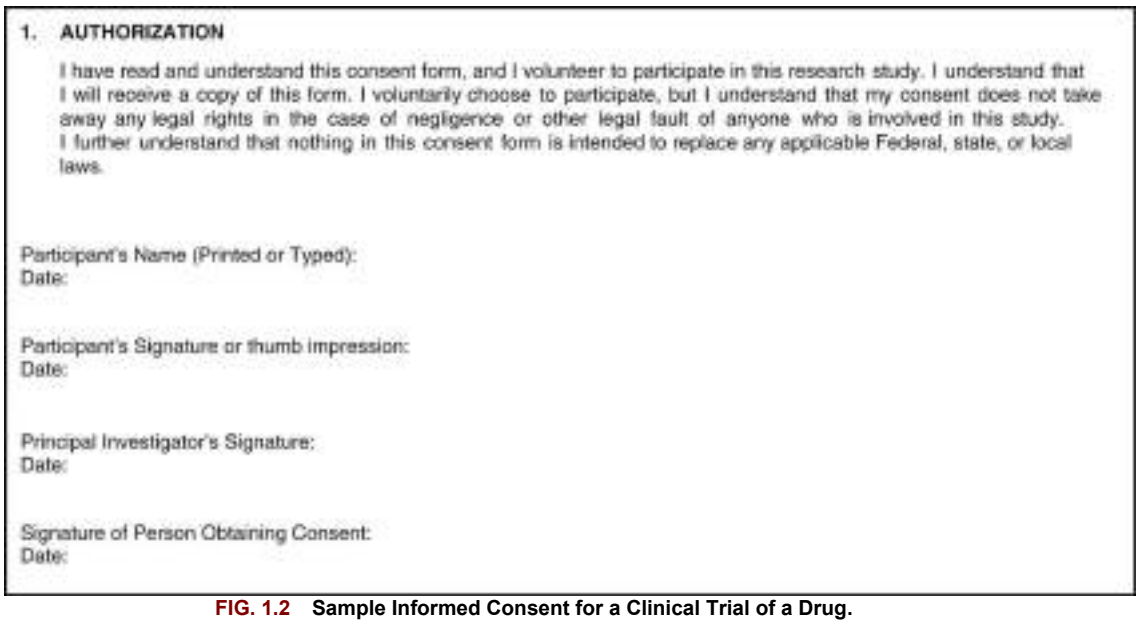
You are free to choose to participate in the study. You may refuse to participate without any loss of benefit which you are otherwise entitled to. You child will receive the same standard care and treatment which is considered best for him irrespective of your decision to participate in the study. You may also withdraw any time from the study without any adverse effect on management of your child or any loss of benefit which you are otherwise entitled to. You may also refuse to answer some or all the questions if you don't feel comfortable with those questions.

Confidentiality

The information provided by you will remain confidential. Nobody except principal investigator will have an access to it. Your name and identity will also not be disclosed at any time. However the data may be seen by Ethical review committee and may be published in journal and elsewhere without giving your name or disclosing your identity.

Available Sources of Information

If you have any further questions you may contact Principal Investigator (Dr. SAK), department of pediatrics at Aga Khan University on following phone number 486xxxx



1. **AUTHORIZATION**

I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to replace any applicable Federal, state, or local laws.

Participant's Name (Printed or Typed):
Date:

Participant's Signature or thumb impression:
Date:

Principal Investigator's Signature:
Date:

Signature of Person Obtaining Consent:
Date:

FIG. 1.2 Sample Informed Consent for a Clinical Trial of a Drug.

From Sample Informed Consent for a Randomized Clinical Trial of a Drug. (n.d.) Aga Khan University. Retrieved from http://www.aku.edu/research/urc/ethicalreviewcommittee/sampleconsentforms/Pages/sampleconsentforms.aspx

BOX 1.2 Informed Consent Checklist: Basic Elements

- 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
- Identification of any experimental procedures
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- For research that involves more than minimal risk, an explanation as to whether any compensation will be paid and whether any medical treatments are available if injury occurs, and if so, what the treatments consist of or where further information may be obtained
- **Research, Rights or Injury**: An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

From Office for Human Research Protections (OHRP). (2014). U.S. Department of Health & Human Services. Retrieved from http://www.hhs.gov/ohrp/policy/consentckls.html

The *experimental group* in drug trials is the group that receives the drug being tested. The *control group* in drug trials may receive no drug; a different drug; a **placebo** (pharmacologically inert substance); or the same drug with a different dose, route, or frequency of administration.

American Nurses Association Code of Ethics

The **American Nurses Association (ANA) Code of Ethics** "was developed as a guide for carrying out nursing responsibilities in a manner consistent with quality in nursing care and the ethical obligations of the profession." It was first adopted in 1950 and most recently was revised with interpretive statements in 2015. The ANA Code of Ethics is founded on the principles first identified by Florence Nightingale, who believed that a nurse's ethical duty was first and foremost to care for the patient. It contains nine provisions (Box 1.3). The 2015 update addresses advances in nursing leadership, social policy and global health, and the challenges nurses face related to social media, electronic health records, and the nurse's expanded role in clinical research.

The Nurse's Role in Clinical Research

Nurses are at the forefront of clinical research. Regardless of the setting (inpatient or outpatient), nurses are likely to encounter patients who are eligible to participate, considering participation, or actively participating in clinical research. As such, nurses are responsible for both the safety of the patient and the integrity of the research protocol.

Nursing Process: Patient-Centered Collaborative Care

Clinical Research

Assessment

- Identify patients who are eligible to participate in or who are participating in clinical research.
- Assess response to the study agent and identify adverse events (an unfavorable or unintended sign, symptom, or disease that was not present at the time of study enrollment and is associated with the treatment or procedure).

Planning

- Have a process in place to identify persons who are eligible to participate in a clinical research or to identify participants actively participating in clinical research studies.
- Have a process in place to facilitate education and informed consent of eligible study participants.
- Plan educational programming for staff who provide direct care to study participants.
- Plan participant care to ensure integrity and compliance with study protocol.

Nursing Interventions

- Support the process of informed consent in a culturally competent manner.
  - Provide an interpreter when necessary.
  - Provide enough time for the person to read the consent and ask questions.
  - Serve as a witness to informed consent.
- After reviewing the study protocol, administer study agent(s).
- Accurately document all participant care, assessment findings, and study agent administration.
- Accurately and safely collect biospecimens.
- Act as advocate, educator, and collaborator in the research process.
  - Ensure safe care.
  - Ensure integrity of study data.
  - Communicate clearly.

Evaluation

- Determine if the potential participant understands what it means to participate in the study by asking open-ended questions.
- Monitor response to the study agent or other interventions.
- Determine whether participants understand how to take their study agents, what to do if they miss a dose, how to store the study agent, and when to call their health care provider.

Drug Standards and Legislation

Drug Standards

The set of drug standards used in the United States is the United States Pharmacopeia (USP). The *United States Pharmacopeia and the National Formulary* (USP-NF), the authoritative source for drug standards (dosage, forms, drug substances, excipients, biologics, compounded preparations, and dietary supplements), is published annually. Experts in nursing, pharmaceutics, pharmacology, chemistry, and microbiology all contribute. Drugs included in the USP-NF have met high standards for therapeutic use, patient safety, quality, purity, strength, packaging safety, and dosage form. Drugs that meet these standards have the initials "USP" following their official name, denoting global recognition of high quality.

The *International Pharmacopeia,* first published in 1951 by the World Health Organization (WHO), provides a basis for standards in strength and composition of drugs for use throughout the world. The book is published in English, Spanish, and French.

BOX 1.3 Provisions of the American Nurses Association Code of Ethics

Provision 1

The nurse practices with compassion and respect for the inherent dignity, worth, and unique attributes of every person.

Provision 2

The nurse's primary commitment is to the patient, whether an individual, family, group, community, or population.

Provision 3

The nurse promotes, advocates for, and protects the rights, health, and safety of the patient.

Provision 4

The nurse has authority, accountability, and responsibility for nursing practice; makes decisions; and takes action consistent with the obligation to promote health and to provide optimal care.

Provision 5

The nurse owes the same duties to self as to others, including the responsibility to promote health and safety, preserve wholeness of character and integrity, maintain competence, and continue personal and professional growth.

Provision 6

The nurse, through individual and collective effort, establishes, maintains, and improves the ethical environment of the work setting and conditions of employment that are conducive to safe, quality health care.

Provision 7

The nurse, in all roles and settings, advances the profession through research and scholarly inquiry, professional standards development, and the generation of both nursing and health policy.

Provision 8

The nurse collaborates with other health professionals and the public to protect human rights, promote health diplomacy, and reduce health disparities.

Provision 9

The profession of nursing, collectively through its professional organizations, must articulate nursing values, maintain the integrity of the profession, and integrate principles of social justice

into nursing and health policy.

From American Nurses Association. (2015). Code of ethics for nurses with interpretive statements. Retrieved from http://nursingworld.org/DocumentVault/Ethics_1/Code-of-Ethics-for-Nurses.html

Federal Legislation

Federal legislation attempts to protect the public from drugs that are impure, toxic, ineffective, or not tested before public sale. The primary purpose of the legislation is to ensure safety. America's first law to regulate drugs was the Food and Drug Act of 1906, which prohibited the sale of misbranded and adulterated drugs but did not address drug effectiveness and safety.

1912: The Sherley Amendment

This act prohibited false therapeutic claims on drug labels. It came about as a result of Mrs. Winslow's Soothing Syrup, a product advertised to treat teething and colic, which contained morphine and led to the death of many infants. Under the Sherley Amendment, the government had to prove intent to defraud before a drug could be removed from the market.

1914: The Harrison Narcotic Act

This act required prescriptions for drugs that exceeded set narcotic limits. It also mandated increased record keeping by physicians and pharmacists.

1938: The Federal Food, Drug, and Cosmetic Act

The Federal Food, Drug, and Cosmetic Act of 1938 empowered the FDA to ensure a drug was safe prior to marketing. It is the FDA's responsibility to ensure that all drugs are tested for harmful effects; it also required that drugs be labeled with accurate information and have detailed literature in the drug packaging that explains adverse effects. The FDA can prevent the marketing of any drug it judges to be incompletely tested or dangerous. Only drugs considered safe by the FDA are approved for marketing.

1951: Durham-Humphrey Amendment

The Durham-Humphrey Amendment distinguished between drugs that could be sold with or without prescription by a licensed health care provider.

1962: Kefauver-Harris Amendment to the 1938 Act

The Kefauver-Harris Amendment resulted from the widely publicized thalidomide tragedy of the 1950s in which European patients who took the sedative-hypnotic thalidomide during the first trimester of pregnancy gave birth to infants with extreme limb deformities. The Kefauver-Harris amendment tightened controls on drug safety, especially experimental drugs, and required that adverse reactions and contraindications must be labeled and included in the literature. The amendment also included provisions for the evaluation of testing methods used by manufacturers, the process for withdrawal of approved drugs when safety and effectiveness were in doubt, and the establishment of effectiveness of new drugs before marketing.

1965: Drug Abuse Control Amendments

Enacted in 1965, the Drug Abuse Control Amendments attempted to control the abuse of depressants, stimulants, and hallucinogens.

1970: The Comprehensive Drug Abuse Prevention and Control Act

In 1970, Congress passed the Comprehensive Drug Abuse Prevention and Control Act. This act, designed to remedy the escalating problem of drug abuse, included several provisions: (1) promotion of drug education and research into the prevention and treatment of drug dependence; (2) strengthening of enforcement authority; (3) establishment of treatment and rehabilitation facilities; and (4) designation of schedules, or categories, for controlled substances according to abuse liability.

Based on their abuse potential and acceptable medical use practices, **controlled substances** are categorized into five schedules, which are listed in Table 1.1. Schedule I drugs are not approved for

medical use and have high abuse potential; schedule II through V drugs have acceptable medical use and decreasing potential for abuse leading to psychological and/or physiologic dependence.

Nurses are key to creating a culture of safety and accountability related to controlled substances. As such, nurses must:

- Verify orders prior to drug administration.
- Account for all controlled drugs.
- Maintain a controlled-substance log that ensures all required information is documented accurately.
- Document all discarded or wasted medication; wastage must be witnessed by another nurse.
- Ensure timely documentation in the patient record following drug administration, including patient response to drug administration.
- Keep all controlled drugs in a locked storage area; keep narcotics under double lock. Be certain that only authorized persons have access to the keys, including keys for patient-controlled analgesia and epidural pumps. Medication may also be administered via an automated dispensing cabinet, with bioidentical identifiers used for access.
- The ANA recognizes the significant threat to patient safety and liability to health care organizations caused by nurse drug diversion and recommends that all states have a peer-to-peer assistance program for addicted nurses. Reporting is mandatory if suspected or known diversion occurs.

1983: The Orphan Drug Act

The Orphan Drug Act was designed to promote the development and manufacture of drugs used in the treatment of rare diseases (orphan drugs). The act's three primary incentives are (1) federal funding of grants and contracts to perform clinical trials of orphan products; (2) a 50% tax credit for costs of clinical testing; and (3) exclusive rights to market the drug for 7 years from the marketing approval date.

1994: Dietary Supplement Health and Education Act

This act established labeling requirements for dietary supplements and authorized the FDA to promote safe manufacturing practices. It classified dietary supplements as food.

1996: Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 protects health insurance coverage for workers who change or lose their jobs and sets the standard for the privacy of individually identifiable health information. The act provides patients more control over their health information, including boundaries on the use and release of health records.

1997: The Food and Drug Administration Modernization Act

The five provisions in this act are (1) review and use of new drugs is accelerated; (2) drugs can be tested in children before marketing; (3) clinical trial data are necessary for experimental drug use for serious or life-threatening health conditions; (4) drug companies are required to give information on off-label (non–FDA-approved) use of drugs and their costs; and (5) drug companies that plan to discontinue drugs must inform health professionals and patients at least 6 months before stopping drug production.

TABLE 1.1

Schedule Categories of Controlled Substances

Schedule	Examples	Description
I	Some examples of substances listed in Schedule I are heroin, lysergic acid diethylamide (LSD), *Cannabis*, peyote, methaqualone, and methylenedioxymethamphetamine (MDMA)	Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.
II	Examples of Schedule II narcotics include hydromorphone (Dilaudid), methadone (Dolophine), meperidine (Demerol), oxycodone (OxyContin, Percocet), and fentanyl (Sublimaze, Duragesic). Other Schedule II narcotics include morphine, opium, codeine, and hydrocodone. Examples of Schedule IIN stimulants include amphetamine (Dexedrine, Adderall), methamphetamine (Desoxyn), and methylphenidate (Ritalin). Other Schedule II substances include amobarbital, glutethimide, and pentobarbital.	Substances in this schedule have a high potential for abuse that may lead to severe psychological or physical dependence.
III	Examples of Schedule III narcotics include products containing not more than 15 mg of hydrocodone per dosage unit (acetaminophen with hydrocodone) or 90 mg of codeine per dosage unit (acetaminophen with codeine), and buprenorphine and naloxone. Examples of Schedule IIIN nonnarcotics include benzphetamine, phendimetrazine, ketamine, and anabolic steroids such as Depo-Testosterone.	Substances in this schedule have a potential for abuse less than substances in Schedules I or II, and abuse may lead to moderate or low physical dependence or high psychological dependence.
IV	Examples of Schedule IV substances include alprazolam, carisoprodol, clonazepam, clorazepate,	Substances in this schedule have a low potential for abuse relative to

	diazepam, lorazepam, midazolam, temazepam, and triazolam.	substances in Schedule III.
V	Examples of Schedule V substances include cough preparations containing not more than 200 mg of codeine per 100 mL or per 100 g (guaifenesin with codeine, promethazine with codeine), and ezogabine.	Substances in this schedule have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.

From Controlled substance schedules. (n.d.). U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control. Retrieved from http://www.deadiversion.usdoj.gov/schedules/#define

2002: Best Pharmaceuticals for Children Act

The BPCA gives manufacturers a 6-month extension of patents to evaluate drugs on the market for their safety and efficacy in children.

2003: Pediatric Research Equity Act

This act authorizes the FDA to require that drug manufacturers test certain drugs and biologic products for their safety and effectiveness in children, noting that "children are not small adults." Additionally, studies that involve children must be conducted with the same drug and in the same disease process as adults.

2007: Food and Drug Administration Amendments Act

This act allows the FDA to do more comprehensive reviews of potential new drugs, mandates postmarketing safety studies, and affects the distribution of drugs found to be not as safe as premarket studies indicated.

2010: Patient Protection and Affordable Care Act

This act was signed into law in 2010 and became effective January 1, 2014. Essential provisions of the reform include (1) quality, affordable health care for all Americans; (2) improved quality and efficiency of health care; (3) prevention of chronic disease and improved public health; (4) improved access to innovative medical therapies; and (5) community living services and supports.

2012: Food and Drug Administration Safety and Innovation Act (FDASIA)

This act was signed into law on July 9, 2012. It strengthens the FDA's ability to safeguard and advance public health by:

- Collecting fees from industry to fund reviews of drugs with the "breakthrough therapy" designation, medical devices, generic drugs, and biosimilar biologic products
- Expediting development of innovative, safe, and effective products
- Increasing stakeholder engagement in FDA processes
- Enhancing the safety of the global drug supply chain