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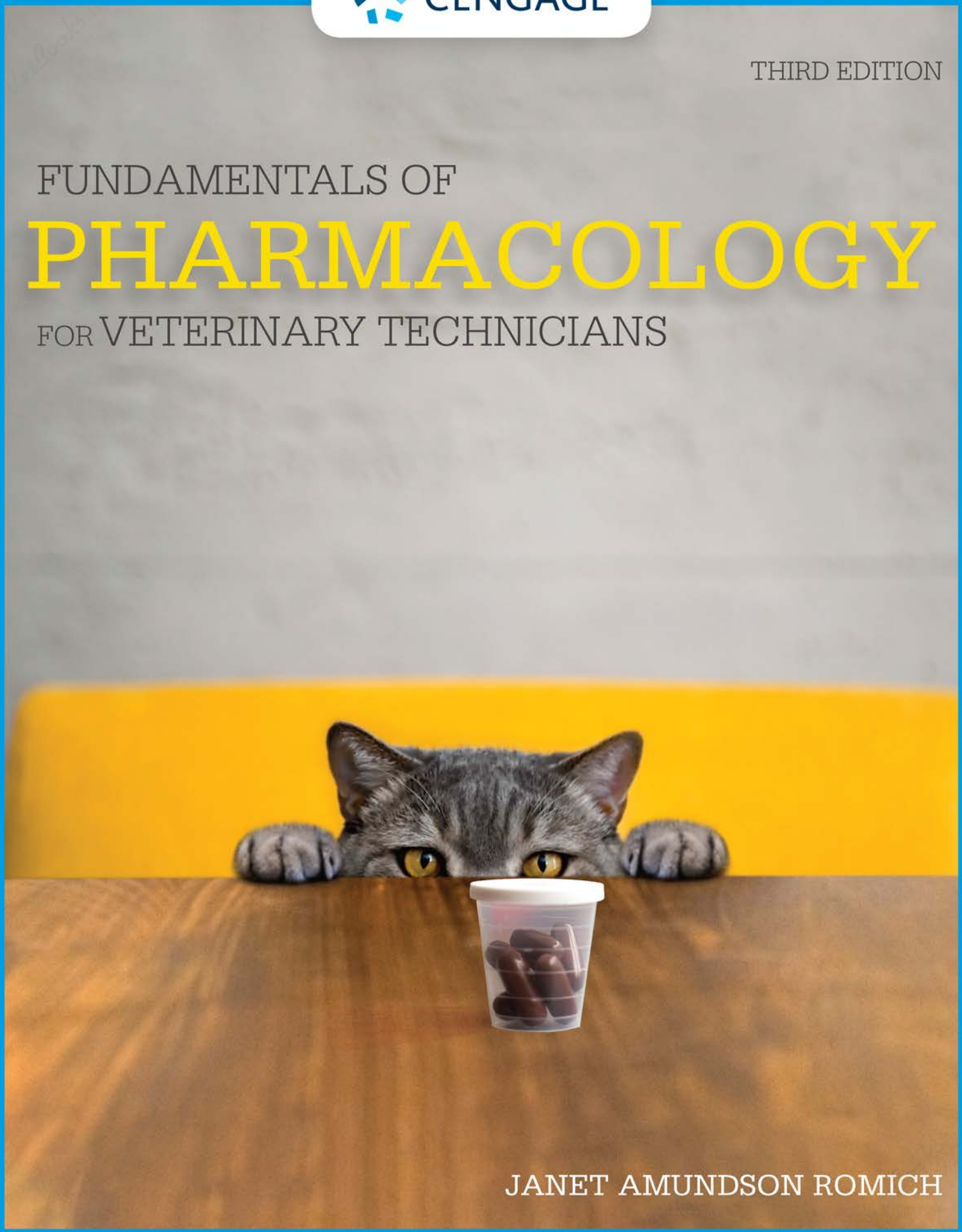
THIRD EDITION

FUNDAMENTALS OF PHARMACOLOGY FOR VETERINARY TECHNICIANS



JANET AMUNDSON ROMICH

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PHARMACOLOGY

FOR VETERINARY TECHNICIANS

Janet Amundson Romich, DVM, MS

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Fundamentals of Pharmacology for Veterinary Technicians, Third Edition
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Library of Congress Control Number: 2019953843

Book Only ISBN: 978-0-357-36147-4

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Printed in the United States of America
Print Number: 01 Print Year: 2020

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PREFACE

Veterinary medicine is an ever-expanding profession that continues to provide opportunities to prevent and treat animal diseases. One of the fields that continues to expand is the discipline of pharmacology. As veterinary professionals, we have already been dragged into the brave new world of pharmaceutical-savvy clients armed with their Internet research on the latest medications available to treat animal diseases because veterinary drugs are now being marketed and sold directly to the consumer. Clients are bombarded with colorful, pop-up ads on the Internet about pain control that also contain testimonials about the superiority of their products over others. Magazines contain full-color ads for drugs such as Frontline® and Cosequin®. Television ads featuring friendly veterinarians discussing flea and tick control with not-so-compliant companion animal owners are now frequently seen by the viewing public.

In addition to marketing techniques used to sell drugs, new categories of drugs, new drug formulations that provide a variety of ways to administer drugs, and new uses for existing drugs continue to be presented in the literature and media on a regular basis. As more clients are willing to treat their animals and manage clinical disease, there has been an increased use of pharmaceutical agents in the veterinary field that has helped manage a variety of medical conditions that occur in veterinary patients.

Despite this enthusiasm, not all animals have an equal chance of being treated for their medical conditions. Although new FDA-approved veterinary drugs continue to be developed, many are not available for all species or clients. For example, pain-relieving drugs may be available for companion animals but not for livestock. Prescription drugs may be too expensive for some clients, and human generic alternatives may not be available or feasible for animal use. Even with the increase in online pharmacies that can purchase drugs in bulk at reduced costs and pass those savings on to clients, some clients cannot afford their animals' prescriptions. Human drug availability has also affected veterinary medicine. The globalization of the human pharmaceutical industry has resulted in drug shortages, as some drugs are only made by one company in a select country. If that company experiences manufacturing problems, the supply of a particular drug quickly diminishes. Human drug abuse has also affected veterinary medicine. The human opioid crisis has altered the availability of some controlled substances that are used in veterinary patients and has put new constraints

on veterinary professionals, such as their participation in Prescription Drug Monitoring Programs to help police the amount of controlled substances a client can get for themselves and their pets.

How are we, as veterinary professionals, preparing ourselves to respond to these changes in the veterinary profession—changes that will require us to stay current in the knowledge of drugs and their applications as well are their marketing, availability, and affordability? The key ingredient in professional preparedness is a good understanding of the fundamentals of pharmacology. This text is designed to give veterinary professionals the solid foundation in pharmacology that the professional habit of staying current in emerging trends in pharmacology is built upon. Building a solid foundation of understanding in pharmacology requires a textbook in an easy-to-read format that provides practical applications of new information and review of concepts, calculations, and critical thinking skills. These applications during a course of study using this text will give student technicians ample opportunity to develop their confidence and proficiency in the area of pharmacology. Developing the confidence in applying pharmacological agents to specific medical uses and acquiring the language needed to explain these uses in both professional and lay terms are considered the benchmark for veterinary professionals.

This textbook and the accompanying learning materials make the process of understanding, applying, and staying current of the changes in pharmacology as straightforward as possible. This textbook presents brief but thorough explanations and reviews of basic terminology, anatomy and physiology, and disease processes needed to understand how drug therapy is utilized. Introductory case studies in each chapter presented as "Setting the Scene," practice calculations throughout the text and on the Student Companion Website and MindTap®, and interesting facts presented as "Clinical Cues" provide the learner with many ways to examine the material presented in pharmacology. Summary sections, tables of drugs described for a variety of medical conditions, and chapter reviews provide the learner guidance in understanding the key points of each pharmacological topic. An introduction to how drugs are developed, made, and delivered to the veterinary community provides the learner with key insights into the world of pharmacology.

About the Author

Dr. Janet Romich received her Bachelor of Science degree in Animal Science from the University of Wisconsin–River Falls, and her Doctor of Veterinary Medicine and Master of Science degrees from the University of Wisconsin–Madison. She worked as a pharmacy technician in both human and veterinary settings while attending veterinary school. Her master's thesis was based on FDA research for a veterinary pharmaceutical company. Dr. Romich has taught a variety of veterinary technician and science courses at Madison Area Technical College in Madison, Wisconsin. Dr. Romich was honored with the Distinguished Teacher Award for her use of technology in the classroom, advisory and professional activities, publication list, and fundraising efforts. She also received the Wisconsin Veterinary Technician Association's Veterinarian of the Year Award for her work in teaching and mentoring veterinary technician students. Dr. Romich has authored the textbooks *An Illustrated Guide to Veterinary Medical Terminology, 4th edition, with MindTap®* and *Understanding Zoonotic Diseases*, as well as co-authored *Delmar's Veterinary Technician Dictionary.* Dr. Romich remains active in veterinary medicine through her relief practice and in research as an Institutional Animal Care and Use Committee member for a hospital research facility.

About the Contributing Author

Dr. Sarah Wagner was born and raised in Wilmington, Delaware. Following a Bachelors of Arts degree in English from Barnard College and a Doctor of Veterinary Medicine degree from Michigan State University, she worked in a mixed animal practice in southwestern Virginia for five years. She completed a PhD in Pharmacology at Iowa State University and is a diplomate of the American College of Veterinary Clinical Pharmacology. She is currently a Professor of Animal Sciences at North Dakota State University in Fargo. Dr. Wagner's interests include food animal pharmacology and dairy cattle health. She has published numerous refereed articles on pharmaceutical use in livestock and is a member of the American Association of Bovine Practitioners, American College of Veterinary Clinical Pharmacology, and Association of Veterinary Technician Educators.

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New to This Edition

The third edition offers new chapter features that include the following:

- An introduction that emphasizes the importance of the chapter content to real-world interactions between veterinary professionals and clients,
- Expanded color artwork to clarify difficult concepts and photos to make connections between disease conditions and the drugs used to manage those conditions,
- End-of-chapter drug tables that describe the drugs presented in the chapter,
- Tables with color coding of veterinary drug trade names (purple) and human drug trade names (orange),
- Generic names of drugs italicized and color coded blue when they first appear in a chapter, and
- Within the body of the text only veterinary drug trade names listed directly after the generic name.

Chapter 1

- Improved descriptions of pharmaceutical terminology including new terms used to describe the role of genes on how animals respond to drug therapy.
- Expanded description of the veterinary/client/patient relationship (VCPR).
- Added discussion of virtual care for animals including definitions and examples of how technology can be used within a VCPR.
- Updated information on controlled substances, drug schedules, and Prescription Drug Monitoring Programs.
- Added information on the Veterinary Feed Directive.
- Example of forms used in veterinary practice are available on the Student Companion Website.

Chapter 2

- Updated tables that clarify the role of regulatory agencies in veterinary pharmacology.
- Graphs added to depict how the therapeutic index relates to drug safety.
- Added information on reporting adverse drug reactions to the FDA and drug manufacturer.
- Additional case study that incorporates a scenario of drug testing in animals.

Chapter 3

- Improved description of the various drug administration routes.
- Added images of routes of drug administration.
- Added descriptions relative to the role veterinary technicians play in drug preparation and administration, such as the use of pill splitters, periodontal fillers, and metered dose inhalers.

Chapter 4

- Updated use of the acronym ADME to help the reader better understand pharmacokinetics.
- Updated description of protein binding in a clinical setting.
- Additional graphic depiction of steady-state concentration.
- Addition of table describing organs of elimination.

Chapter 5

- Expanded description of drug compounding including description of adulterated drugs.
- Updated drug references including veterinary digital resources as well as human digital databases.
- Added examples of electronic software and its use in electronic medical record keeping, prescription label generation, and inventory management.
- Added description of inventory shipment information to include free on board (FOB) destination and FOB shipping point.
- Added information on disposal of unused/unwanted drugs.
- Examples of Safety Data Sheets available on the Student Companion Website.

Chapter 6

- Added dilution examples of commonly used solutions such as chlorhexidine and bleach.
- Added information about the concept of quantity sufficient.

Chapter 7

- Updated information about opioid categories and controlled substance schedules.
- Added table on opioids and their use and duration of action in providing analgesia.
- Added clinical examples of ceiling effect (buprenorphine) and dual dosing (dopamine and dobutamine).
- Expanded coverage of inhalant anesthetics to include solubility via the blood–gas partition coefficient and vapor pressure.
- Expanded descriptions of sympathetic nervous system drugs especially as they pertain to anesthesia.
- Added information about constant rate infusions (CRIs) in a new appendix to complement this chapter.

Chapter 8

- Expanded description of cardiac output and an animal's adaptations to decreased cardiac output.
- Added figure describing factors affecting blood pressure and the clinical effects they produce.
- Expanded description of congestive heart failure.
- Updated information on antiarrhythmic drugs.

Chapter 9

- Expanded information on nebulizers and metered dose inhalers including their care to prevent contamination.
- Expanded descriptions of asthma, recurrent airway obstruction in horses (formerly known as chronic obstructive pulmonary disease), infectious tracheobronchitis (kennel cough), bovine respiratory disease, and pulmonary edema.

Chapter 10

- Updated information on diabetes mellitus and the types of insulin available for veterinary use.
- Updated information on drugs available to treat hyperadrenocorticism and pituitary pars intermedia dysfunction.
- Updated information regarding anabolic steroid availability.
- Updated information on the use of growth promotants in livestock.
- Updated information on drugs used for estrus synchronization in animals.

Chapter 11

- Updated terminology to include orexigenic drugs as well as descriptions about clinical signs of gastrointestinal (GI) diseases such as obstipation and constipation.
- Added description of the enteric nervous system.
- Expanded description of veterinary dental products including topically applied antibiotic drugs.
- Expanded description of drugs used to stimulate an animal's appetite.
- Added description of equine colic and illustration of common impaction sites in horses.

Chapter 12

- Expanded description of urolith management.
- Expanded description of carbonic anhydrase inhibitors.
- Added description of angiotensin receptor blocker.

Chapter 13

- Added warning about accidental injection of neuromuscular blocking agents.

Chapter 14

- Added description of concepts of antibiotic drug use including breakpoints and antibiotic drug resistance.
- Added information about the judicious use of antimicrobial drugs.
- Added information about antimicrobial growth promotants.

- Expanded information on bacteria commonly identified in veterinary patients.
- Added information about antiviral drugs used in veterinary medicine.
- Updated description of disinfection including information on product labels, cleaning and disinfecting protocols, and accelerated hydrogen peroxide products.
- Additional tables containing information on antimicrobial drugs used in various species is available on the Student Companion Website.

Chapter 15

- Added description of parasitic control methods including FAMCAHA® and fecal egg count reduction testing (FECRT).
- Updated ectoparasitic drugs section.
- Expanded description of adverse drug reactions to antiparasitic drugs (e.g., MDR1 mutation in collie and collie-type dogs, feline reactions to pyrethrins, topical spot-on reactions, etc.).
- Additional tables containing information on antiparasitic drugs used in various species is available on the Student Companion Website.

Chapter 16

- Expanded description of selective COX-2 inhibitors.
- Added descriptions of new FDA-approved nonsteroidal anti-inflammatory drugs (NSAIDs).
- Expanded descriptions of analgesics used in veterinary medicine including the use of ketamine CRIs, local anesthetics, and transdermal applications of analgesics.
- Expanded descriptions of immunomodulators to include oclacitinib, piroxicam, and tacrolimus.

Chapter 17

- Added description of hoof health and management of hoof conditions such as hairy heel wart and foot rot.
- Added description of conditions of uncontrolled growth such as proud flesh and sarcoids in horses.
- Added descriptions of oral antipruritic drugs such as oclacitinib, lokivetmab, and cyclosporine.

Chapter 18

- Added description of intracameral and intravitreal injections.
- Added information of otic preparations that have a longer duration of action with a single application.

Chapter 19

- Updated information on potassium supplement limitations to avoid bradycardia.
- Updated information on dosages of emergency drugs when administered intratracheally.
- Updated information and photos on labeling fluids for administration.
- Added description on advanced life support.
- Added description of cardiac pump versus thoracic pump theory of chest compressions during cardiopulmonary cerebral resuscitation (CPCR).
- Expanded descriptions of emergency drugs.
- Additional table about oxygen supplementation methods.

Chapter 20

- Added description of goals of chemotherapy differentiating remission versus palliative care.
- Added description of adverse effects of antineoplastic drugs.
- Expanded description of administering and handling of antineoplastic drugs.
- Added description of cancer pain and its management.
- Added description of paraneoplastic syndromes.
- Expanded description of immunomodulatory drugs.
- Added description of the melanoma vaccine.

Chapter 21

- Expanded description of primary and secondary immune responses.
- Expanded description of feline injection site sarcomas.
- Added description of vaccine claims and new vaccine labeling requirements.
- Updated lists of vaccines available for various animal species.

Chapter 22

- Added descriptions of anxiety and fear and their relationship to abnormal behaviors.
- Updated uses for behavior-modifying drug categories.

Chapter 23

- Updated description of commercially available sources of herbal supplements.
- Added information about cannabis available at the time of publication.
- Added information about the National Animal Supplement Council (NASC) Quality Seal.

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CHAPTER 1

A Brief History of Veterinary Pharmacology

OBJECTIVES

Upon completion of this chapter, the reader should be able to:

1.1 describe the history of pharmaceuticals and their development.
1.2 define key terms used in pharmacology.
1.3 describe the FDA's role in drug approval.
1.4 describe the FDA's role in monitoring drug safety.
1.5 differentiate between the use of prescription drugs, over-the-counter drugs, extra-label drugs, and controlled substances.
1.6 describe the use of withdrawal times and the prevention of drug residues in food-producing animals.
1.7 describe a veterinarian/client/patient relationship.
1.8 explain the differences between C-I, C-II, C-III, C-IV, and C-V controlled drugs.

KEY TERMS

biologics
controlled substance
drug
Drug Enforcement Administration (DEA)
drug residue
electronic prescribing (E-prescribing)
extra-label drug use (ELDU)
Food and Drug Administration (FDA)
indication
over-the-counter (OTC) drugs
pharmaceutical
pharmacodynamics
pharmacokinetics
pharmacology
pharmacogenetics
pharmacogenomics
pharmacotherapeutics
pharmacotherapy
prescription drugs
telehealth
veterinarian/client/patient relationship (VCPR)
withdrawal time/withholding time

Setting the Scene

The owner of a sick dog comes into a veterinary clinic seeking treatment for the animal. The owner is depending on the veterinarian to prescribe drugs that will effectively treat the dog's illness, yet be safe for the dog and manufactured properly. How can this owner be sure that the drugs prescribed for his dog are safe and effective? How can the veterinary technician convince this owner that this is true? Can explaining how the FDA evaluates drugs for efficacy and safety prior to approval and oversees drug manufacturing after drugs are approved address this client's concerns? What agencies regulate drugs? Are all drugs regulated in the same way?

Introduction

Veterinary professionals use their knowledge of pharmacology to understand how drugs work in an animal's body, select appropriate drugs to achieve intended therapeutic effects, and anticipate potential adverse effects. When providing patient care, veterinary technicians are often closest to the patient and best able to assess both the patient's condition prior to administration of the medication and the patient's response to the medication. Veterinary technicians also interact with owners who may tell them information about an animal's condition first or in a different way than they do to a veterinarian. Veterinary technicians with an in-depth understanding of when and how medications are best used and the expected responses are able to provide optimal care to their patients and accurate, timely, and useful client education.

A History of Veterinary Pharmacology

Veterinary medicine has existed since ancient times, as evidenced by archeological ruins in India of a hospital for horses and elephants that operated in 5000 B.C. However, *veterinary pharmacology*—the study and use of drugs in animal health care—is a much younger specialty. Its origins are traced to the early 1700s, when multiple epizootics (an epidemic within an animal population) in western Europe destroyed most of its cattle population. The first outbreak, which occurred in 1709, was rinderpest, a fatal and highly contagious viral disease causing fever, anorexia, and ocular discharge in cattle. The second outbreak which occurred in 1712, was anthrax, a fatal bacterial disease causing rapid death in cattle and potentially causing disease in humans. The third outbreak occurred in 1755 from foot-and-mouth disease, a highly contagious viral disease causing fever and blisters in cloven-hooved animals. Europeans realized, in the wake of these catastrophes, how little anyone knew about animal diseases. In France, this concern led to the establishment of five veterinary colleges in the 1760s. Austria, Germany, the Netherlands, England, and Scotland followed France's lead in the late 1790s and established their own veterinary colleges. By the 1850s, veterinary colleges were being organized in America, with a veterinary college opening in Philadelphia in 1852 and another one opening in Boston in 1854. There are currently 30 colleges of veterinary medicine in the United States with accreditation by the American Veterinary Medical Association (AVMA), along with 5 in Canada, 1 in Mexico, and more than a dozen outside North America.

What did the establishment of veterinary colleges have to do with the birth of veterinary pharmacology? Veterinary colleges were founded as adjuncts to schools of medicine, which taught *materia medica*, the study of the physical and chemical characteristics of materials used as medicines. Originally, these medicines were derived from plants or their components. As scientists extracted and synthesized more sophisticated drugs from these plant components, *materia medica* gave way

Table 1-1 Original Drug Sources

Drug Source	Example
Minerals	Sulfur, iron, electrolytes
Botanical (from plants)	Digitalis, opioids
Animal	Insulin, thyroid hormone, lanolin
Synthetic (manmade or engineered)	Aspirin, steroids, procaine
Biological (from molds or bacteria)	Antibiotics, ergot

to a new field called pharmacology and veterinary *materia medica* became veterinary pharmacology. Many drugs used today were originally derived from plants, bacteria, and animal sources (Table 1-1). Several anticancer drugs have been discovered in plants, most antibiotics have been discovered in soil bacteria, and many hormonal drugs are processed from animal tissue. These natural substances may now be made semi-synthetically, with substances chemically modified from a natural source or manufactured based on the understanding of the chemicals found in the original plant product. The vast majority of drugs currently in use are made by entirely synthetic means, through chemical reactions in a laboratory. These agents are synthesized after determination of how the chemical structure of a compound relates to its pharmacological properties. Because synthetic drugs are made in the laboratory, they tend to have greater purity than those that are naturally derived.

Clinical Cue

The U.S. Food and Drug Administration (FDA) defines a **drug** as "A substance (other than food) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." Drugs can be therapeutic (e.g., antihistamines used to treat clinical signs of allergies), curative (e.g., antibiotics that kill bacteria), replacement (e.g., thyroid hormone given to animals that do not produce enough hormone), preventive (e.g., ivermectin to prevent infestation by the parasite that causes heartworm disease), or diagnostic (e.g., radiopaque drugs used in conjunction with radiology to determine the location of a disease process). Drugs are "intended to affect the structure or any function of the body"; therefore, they can positively affect an animal's health if given appropriately (such as giving the proper antibiotic to kill bacteria in a patient with bacterial pneumonia) or can negatively affect the animal if given inappropriately (such as giving an antibiotic to a patient with a viral infection).

Pharmaceutical Terminology

Understanding pharmaceutical terms is fundamental to understanding pharmacology. The root *pharmaco-* is Greek for "drug" or "medicine"; therefore, the term **pharmacology** is the study of drugs (-logy is the suffix that means "study of"). *Pharmakeutikos* is the Greek word for "druggist"

or someone who produces medicine; therefore, the term **pharmaceutical** is the science, preparation, and production of drugs. *Pharmacotherapeutics*, *pharmacokinetics*, and *pharmacodynamics* are three terms that are used to explain the mechanics of veterinary pharmacology. *Pharmacogenetics* and *pharmacogenomics* are terms that describe how genes and genetic variation influence an animal's response to a drug.

Pharmacotherapy is the treatment of disease with medicines. The use of medicine to treat disease has been prevalent for thousands of years. Hippocrates revolutionized medicine in ancient Greece by using medicines to heal illness. The use of antibiotics to treat a skin infection in dogs is an example of pharmacotherapy.

Pharmacotherapeutics is the field of medicine that studies drug use in the treatment of disease. Veterinary pharmacotherapeutics involves investigating how a sick animal responds to drugs.

Pharmacokinetics is the study of the physiological movement of drugs within the body (*kinetics* is the medical term for the scientific study of motion). Pharmacokinetics includes the study of the absorption, distribution, metabolism (or biotransformation), and elimination (excretion) of drugs. Understanding pharmacokinetics helps determine how quickly the medicine is absorbed after administration, how quickly it travels through the body to the desired site of action, how long that medicine stays in the animal's body, and how the drug leaves the body. Pharmacokinetic data enable us to determine how much of a drug should be given, by what route, and when, to maximize the effectiveness of drug treatment. Chapter 4 will take a closer look at the principles of pharmacokinetics.

Pharmacodynamics is the study of the mechanisms of drug action and involves understanding the interactions between the chemical components of living systems and the drugs that enter those systems. All living organisms function by a series of complicated, continual chemical reactions, and when a new chemical enters the system, multiple changes in cell function may occur. Veterinary pharmacodynamics involves the study of a healthy animal's response to drugs to determine drug effects on the physiological and biochemical systems of the body. Understanding the interaction between a drug and its receptor is an example of pharmacodynamics. Clinically, pharmacodynamics is used to avoid drug interactions and minimize the adverse effects that may result when drugs are administered to an animal.

Clinical Cue

Think of pharmacodynamics as "what the drug does to the body" and pharmacokinetics as "what the body does to the drug."

Pharmacogenetics is the branch of pharmacology that studies variation in drug response and/or drug behavior based on an individual's genetic makeup; basically it is how variation in one single gene influences the response to a drug. Pharmacogenetics can help explain adverse (undesirable) drug reactions unique to a patient or breed of animal (such as ivermectin sensitivity in collie dogs) and can be used to create individualized drug therapies for veterinary patients. The current benefit of pharmacogenetics is that information about any breed-related adverse drug reactions is available to veterinarians so they can make appropriate decisions about drug therapy.

Pharmacogenomics is the study of the impact of genetic variation on drug effects and involves studying the whole genome (genes in all chromosomes); basically it is how all of the genes (the genome) can influence responses to drugs. The goal of pharmacogenomics is personalized medicine based on genetic tests to determine if an animal has the necessary enzyme to metabolize a specific drug, and then using that information to individualize the dosage for each patient.

Clinical Cue

Pharmacogenomics can explain why some breeds react differently to a drug than other breeds. For example, some dogs have variable activity of the enzyme thiopurine methyltransferase (TPMT). Dog breeds such as giant schnauzers have significantly lower TPMT activity, while Alaskan malamutes have higher TPMT activity. Drugs such as azathioprine can be metabolized to inactive substances by TPMT, which suggests that giant schnauzers who have lower TPMT levels are susceptible to adverse effects of azathioprine, while malamutes who have higher TPMT levels may not gain any benefit from the medication.

Regulation of Drug Products

The U.S. **Food and Drug Administration (FDA)** became a government agency to enforce the federal Pure Food and Drugs Act of 1906. Before 1906, drug manufacturers had no obligation to establish the safety, purity, or effectiveness of their drugs; therefore, many questionable or even harmful products were legally sold. The Pure Food and Drug Act of 1906 established standards for drug strength and purity and guidelines for drug labeling.

During its first three decades of operation, the FDA was a small agency with limited influence and authority. The drugs available in that era were primarily from botanical (plant) and biological (molds or bacteria) sources. Public concern focused on three botanical drugs: ergot, a derivative of rye fungus used to induce labor and treat migraines; quinine, a derivative of tree bark used to treat malaria; and digitalis, a derivative of the foxglove plant used to treat cardiac failure. All three drugs perform well if correctly dosed, but all are quite toxic if overdosed. At that time, dosing and overdosing were frequently a matter of trial and error. The FDA had little power to determine and enforce correct dosage information, and in 1933, the FDA introduced a bill to revise and strengthen the 1906 Pure Food and Drug Act. A five-year legislative battle ensued, until a drug disaster occurred. In 1937, the antibiotic drug elixir sulfanilamide was distributed in a vehicle of diethylene glycol (a vehicle is a substance in which a drug's active agent is formulated), which was never tested for safety on people or animals prior to being sold as a drug. It turns out that diethylene glycol is toxic to people; as a result of taking elixir sulfanilamide, over 100 people died, many of them children. To help regulate drug dosing and improve drug safety, Congress passed the Federal Food, Drug, and Cosmetic Act in 1938, which required that a drug be adequately tested to demonstrate its safety when used as its label directs. The Act also prohibited false therapeutic claims and established the inspection of drug manufacturing facilities by the federal government. The 1938 law greatly expanded the power and responsibilities of the FDA, and this expansion continued in the postwar years, as chemicals became widely used for drugs, cosmetics, food additives, and pesticides. In 1972, the Act was amended to include many more protections, such as over-the-counter (OTC) drug review, to enhance the safety, effectiveness, and labeling of drugs sold without a prescription.

Clinical Cue

Although the FDA regulates the development and sale of drugs in the United States, local laws further regulate the distribution and administration of drugs. In most cases, the strictest law is the one that prevails in legal proceedings.

Clinical Cue

It is important to note that FDA regulations do not cover certain medically significant compounds known as **biologics** (therapeutic agents derived from living organisms, such as vaccines, antibodies, and toxoids). Biologics are governed by U.S. Department of Agriculture (USDA) regulations and are brought to market differently than how drugs are brought to market.

The Center for Veterinary Medicine

The FDA is headed by a commissioner and organized into a number of different centers, each performing a specific function. The FDA's Center for Veterinary Medicine (CVM) ensures that approved veterinary medicines will not harm animals, or at least that the harm a drug produces will be outweighed by its benefit. The FDA's CVM prohibits the sale and use of a drug that would cause animals to suffer serious health problems. For example, a dog with tachycardia (rapid heartbeat) is given a pill that returns the heartbeat to a normal rate within two hours. When the dog eats a bowl of food, the heart medication causes him to vomit, making him feel poorly again, but for a different reason. The drug that corrected the dog's tachycardia made him vomit and feel very uncomfortable. The FDA's CVM would determine whether the discomfort caused by the medication was acceptable in comparison to the benefit of lowering the dog's heart rate. In this case, if the vomiting subsides and causes minimal discomfort, the drug's ability to slow the heartbeat far outweighs the unpleasant but tolerable adverse effect of vomiting. The FDA would approve this drug and alert medical professionals of the adverse effects of the drug. The FDA thus strives to protect consumers, health professionals, and animals by maximizing the benefit of drugs while minimizing their dangers.

Clinical Cue

An idiosyncratic reaction (an abnormal response to a drug that is peculiar to an individual animal and unrelated to the drug dosage) does not cause the FDA to disapprove a drug. FDA approval of a particular drug is based on the drug's therapeutic effects and adverse effects in many test animals.

The FDA's power to protect veterinarians and animals is a result of the 1968 amendments to the Act concerning "New Animal Drugs." These amendments require a drug manufacturer to demonstrate that its drug is safe for animals and does what the label claims. However, the 1968 amendments also affect veterinarians in a completely different way: Drug manufacturers must now calculate and state on the drug label the withdrawal time (also called withholding time), which is the period following the last drug dose during which the animal or its products (e.g., milk, eggs, or honey) may not be sold for human consumption. Observing label dosing regimens and withdrawal times ensures that animals and their products will be free of illegal drug contamination. These provisions were developed to assure consumers that dairy, poultry, and meat products do not contain drug residues above tolerance limits, which range from zero to levels in the range of parts per million. Since the 1968 amendments, veterinarians must instruct livestock owners about the laws governing any drugs administered to their animals.

Figure 1-1 provides a timeline for drug regulation in the United States.

1906	The original Pure Food and Drug Act is passed by Congress on June 30 and signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods and drugs. The Meat Inspection Act is passed the same day (this Act was passed due to concern over insanitary conditions in meatpacking plants and the use of poisonous preservatives and dyes in foods).
1914	The Harrison Narcotic Act imposes upper limits on the amount of opium, opium-derived products, and cocaine allowed in products available to the public; requires prescriptions for products exceeding the allowable limit of narcotics; and mandates increased record-keeping for physicians and pharmacists that dispense narcotics.
1933	FDA recommends a complete revision of the obsolete 1906 Pure Food and Drug Act. The first bill is introduced into the Senate, launching a five-year legislative battle.
1937	Elixir of sulfanilamide, containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom are children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.
1938	The federal Food, Drug, and Cosmetic Act of 1938 is passed by Congress, containing new provisions such as authorizing factory inspections and requiring new drugs to be shown safe before marketing. This act started a new system of drug regulation.
1941	FDA drastically revises manufacturing and quality control standards due to nearly 300 deaths and injuries as a result of distribution of sulfathiazole tablets tainted with the sedative phenobarbital. The incident prompts the beginning of good manufacturing practices (GMPs).
1951	Durham-Humphrey Amendment defines the kinds of drugs that cannot be used safely without medical supervision and restricts their sale to prescription by a licensed practitioner.
1965	Drug Abuse Control Amendments are enacted to deal with problems caused by abuse of depressants, stimulants, and hallucinogens.
1968	Animal Drug Amendments place all regulation of new animal drugs under one section of the Food, Drug, and Cosmetic Act (Section 512) making approval of animal drugs and medicated feeds more efficient.
1970	The Comprehensive Drug Abuse Prevention and Control Act replaces previous laws and categorizes drugs based on abuse and addiction potential.
1970	Environmental Protection Agency established; takes over FDA program for setting pesticide tolerances.
1972	Over-the-Counter Drug Review is initiated to enhance the safety, effectiveness, and appropriate labeling of drugs sold without prescription.
1972	Regulation of biologics (including serums, vaccines, and blood products) is transferred from National Institutes of Health to FDA. The Food Security Act of 1985 gave regulation of biologics to the USDA.
1983	Orphan Drug Act passed, enabling FDA to promote research and marketing of drugs needed for treating rare diseases.
1984	Drug Price Competition and Patent Term Restoration Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective.
1988	Generic Animal Drug and Patent Term Restoration Act extends to veterinary products benefits given to human drugs under the 1984 Drug Price Competition and Patent Term Restoration Act. Companies can produce and sell generic versions of animal drugs approved after October 1962 without duplicating research done to prove them safe and effective. The act also authorizes extension of animal drug patents.
1994	Dietary Supplement Health and Education Act establishes specific labeling requirements, provides a regulatory framework, and authorizes FDA to mandate good manufacturing practice regulations for dietary supplements. This act defines "dietary supplements" and "dietary ingredients" and classifies them as food.
1994	Animal Medicinal Drug Use Clarification Act (AMDUCA) allows veterinarians to prescribe extra-label use of veterinary drugs for animals under specific circumstances. In addition, the legislation allows licensed veterinarians to prescribe human drugs for use in animals under certain conditions.
1996	Animal Drug Availability Act adds flexibility to animal drug approval process, providing for flexible labeling and more direct communication between drug sponsors and FDA. The Veterinary Feed Directive (VFD) is part of this Act, which identifies drugs that need approval by a veterinarian for use in animal feed. This prevented all commercially available animal drugs for use in medicated feeds to be available for over-the-counter purchase and gave the FDA's CVM more control of the use of animal feed additives.
1997	Food and Drug Administration Modernization Act reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices, advertising unapproved uses of approved drugs and devices, health claims for foods in agreement with published data by a reputable public health source, and development of good guidance practices for agency decision-making.

Figure 1-1 Chronology of drug regulation in the United States. (Adapted from A History of the FDA and Drug Regulation in the United States at http://www.fda.gov) *(Continued)*

2001	Minor Use and Minor Species Health Act is similar to the human Orphan Drug Act of 1983. It is intended to provide FDA-authorized drugs for those less common species and indications (provides labeled drugs for needy minor species and provides major species (cats, dogs, horses, cattle, swine, turkey, chickens) with needed therapeutics for uncommon indications called minor uses). The Minor Use and Minor Species Animal Health Act encourages the development of treatments for species that would otherwise attract little interest in the development of veterinary therapies.
2003	The Animal Drug User Fee Act (ADUFA) permits FDA to collect subsidies for the review of certain animal drug applications from sponsors, analogous to laws passed for the evaluation of other products FDA regulates, ensuring the safety and effectiveness of drugs for animals and the safety of animals used as foodstuffs.
2008	The Animal Generic Drug User Fee Act (AGDUFA) permits FDA to study ways to improve the timeliness and predictability of the animal generic drug review process. The goals are to shorten the time to review and act on submissions by increasing staff and resources.
2011	Food Safety and Modernization Act (FSMA) gives the FDA new enforcement authorities related to food safety standards, provides the FDA tools to hold imported foods to the same standards as domestic foods, and directs FDA to build an integrated national food safety system in partnership with state and local authorities.
2013	Drug Quality and Security Act (DQSA) was enacted following a 2012 deadly outbreak of fungal meningitis in people that was linked to a compounded glucocorticoid. DQSA gives the FDA more authority over compounded drugs by outlining steps for an electronic and interoperable system to identify and trace certain prescription drugs throughout the United States.
2017	Veterinary Feed Directive (VFD) is updated to include veterinarian engagement with the client, examination of the patient and/or visit to the facility where the patient is managed, and provision of necessary follow-up evaluation or care when creating and maintaining a VCPR.

Figure 1-1 *(Continued)*

Categories of Drug Products

Some drugs are available without a prescription for treating a variety of conditions. These drugs are referred to as **over-the-counter (OTC) drugs** and may be purchased by the client without a prescription. Some of these drugs were approved as prescription drugs but later were found to be safe and useful in patients without the need of a prescription. Some of these drugs were not rigorously screened and tested by the current drug evaluation protocols because they were approved prior to the creation of current standards. In 1972, the Over-the-Counter Drug Review was initiated to enhance the safety, effectiveness, and labeling of OTC drugs. Many OTC drugs do not have a significant potential for toxicity when "taken as directed" nor do they require special administration; however, there are several problems related to OTC drug use. These problems include the drug's potential to mask the signs of underlying disease, making diagnosis more difficult; to interact with prescription drug therapy; and to cause serious complications if they are not taken as directed. For example, bismuth subsalicylate (Pepto-Bismol®) is a common OTC human antidiarrheal drug, which may occasionally be used in veterinary medicine. In order to avoid toxic effects, bismuth subsalicylate must be given less frequently in dogs than it is given in humans. Subsalicylate is an aspirin-like product, and because cats do not rapidly metabolize aspirin, Pepto-Bismol® should be used cautiously or not at all in cats. Examples of veterinary OTC drugs include nutritional supplements such as glucosamine and chondroitin and some topical flea and tick products. Veterinary OTC drugs have label information for specific animal species, health concerns, and administration guidelines, which owners should follow or seek the advice of their animal's veterinarian. Figure 1-2 is an example of an OTC drug label.

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A list of FDA-approved animal drug products can be found on the FDA web site at https://www.fda.gov/animalveterinary/products/approvedanimaldrugproducts/.

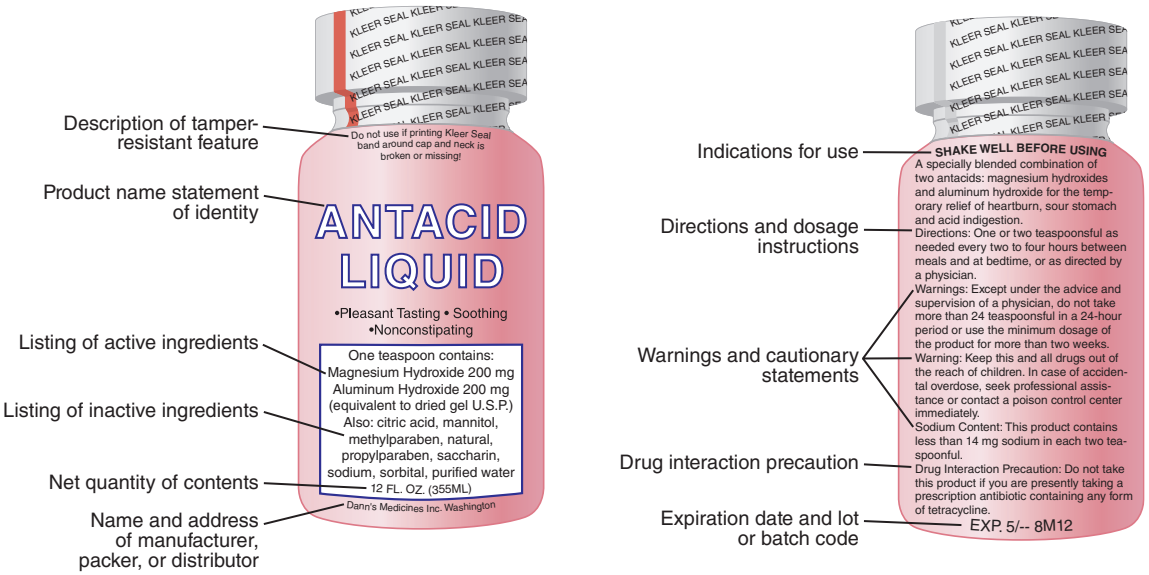

Figure 1-2 Example of an over-the-counter drug label.

Every drug has the potential to cause harm (if given for the wrong reason, to the wrong animal, or in the wrong amount); therefore, drugs must be regulated to ensure their safe use. **Prescription drugs**, which the FDA regulates, are limited to use under the supervision of a veterinarian or physician because of potential toxicity concerns, administration difficulty, or other considerations. Prescription drugs for animals can be obtained from a veterinarian or from a pharmacy pursuant to a prescription issued by a veterinarian. Prescription drugs must be labeled with the statement or legend: "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian." Figure 1-3 is an example of a prescription drug label.

Before a prescription drug can be prescribed for an animal, a **veterinarian/client/patient relationship (VCPR)** must exist. The AVMA recognizes the existence of a VCPR when:

- the veterinarian has assumed the responsibility for making clinical judgments;
- the client has agreed to follow the veterinarian's instruction;
- the veterinarian has sufficient knowledge of the animal to make the diagnosis because he or she is personally acquainted with the keeping and care of the animal based on a timely examination or medically appropriate and timely visits to the operation where the animal is managed;
- the veterinarian is available for follow-up evaluation in the event of an adverse reaction or failure of treatment,
- the veterinarian provides oversight of treatment, compliance, and outcome; and
- patient records are maintained.

There is no universal standard for how recently or often an animal must be examined by the veterinarian in order for a valid VCPR to exist. In companion animals, it is generally agreed that the pet must be physically examined by a veterinarian at the outset of care, but changes to the therapeutic regimen as the case progresses may not always require repeated examinations. Among livestock species, individual examination of each animal prior to treatment is not always considered necessary for the VCPR to be valid, provided that the veterinarian regularly visits the farm premises, communicates with the people who manage the animals, and is familiar with the management practices on the farm where the animal is kept. An established VCPR may be maintained through virtual care, which includes interaction between veterinarians, clients, and patients using any form of technology to deliver patient care. The term for the overarching care that encompasses use of all technologies