A Non-Sterile Compounding Overview: Summarizing USP <795>

Lauren Eichstadt, PharmD

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ACTIVITY DESCRIPTION

Compounding is essential for treating patients that have unique needs preventing the "one-size fits all" approach of approved products. These patients often include pediatric and veterinary patients, but can include adults as well. Despite the need for pharmacists to compound, compounding is being pushed aside in pharmacy school curriculum to make room for other topics resulting in new graduates with little compounding knowledge. This CE provides practicing pharmacists and pharmacy technicians with the basic information essential to compound capsules, suspensions and transdermal products for their patients. A review of USP 795 requirements, compounding resources, and general considerations for compounding different dosage forms for different types of patients will be included.

TARGET AUDIENCE

The target audience for this activity is **pharmacists** and **pharmacy technicians** in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES

After completing this activity, the **pharmacist** will be able to:

- Explain the difference between compounding and manufacturing
- Determine the beyond-use-date of compounded formulations
- Summarize USP <795> requirements for compounding capsules and liquids
- Evaluate a prescription for compounding appropriateness
- Determine if a given compound is appropriate for a veterinary patient

After completing this activity, the **pharmacy technicians** will be able to:

- Identify appropriate quality control tests that should be performed on every compound
- Identify steps where compounding errors can occur
- List visual inspection techniques for compound stability

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ABOUT THE AUTHOR

Dr. Eichstadt graduated from the University of Findlay, College of Pharmacy with her PharmD degree in May 2015. In June 2015, she started at Purdue University Veterinary Teaching Hospital as their first veterinary pharmacy resident making her one of four residents in the country with this title. Throughout her residency, Dr. Eichstadt completed multiple research projects including one on compounded transdermal fluoxetine for feline patients. Dr. Eichstadt also was actively involved in compounding medication for hospital patients and teaching pharmacy and veterinary students. Dr. Eichstadt completes her residency on June 30, 2016, and will be starting as a staff pharmacist at UC Davis, Veterinary Teaching Hospital Pharmacy on August 1, 2016. In her spare time, Dr. Eichstadt competes with her Quarter Horses Lucky and Banjo in hunter and equitation events at the national level.

Lauren Eichstady, PharmD,
Purdue Veterinary Teaching Hospital

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Introduction

Compounding is defined as,[1]

> The preparation of components into a drug product (1) as the result of a practitioner's prescription drug order based on the practitioner/patient/pharmacist relationship in the course of professional practice, or (2) for the purpose of or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing.

In contrast, manufacturing is defined as,[1]

> The production, preparation, propagation, conversion or processing of a drug or device, either directly or indirectly, by extraction from substance of natural origin or independently by means of chemical or biological synthesis. Includes the packaging or repackaging of a drug or device or the labeling or relabeling of the container of a drug or device for resale by pharmacies, practitioners, or other persons.

The principle difference between the definitions of compounding and manufacturing is the requirement that compounding is based on a prescription or in anticipation of prescriptions within a pharmacy whereas manufacturing is performed on a large scale and is not patient-specific. The exception is compounding for office use. Some states allow pharmacists to compound medications for office use. Individual state laws should be consulted for details. The key is that compounding should never look like manufacturing. Manufacturers are required to adhere to Good Manufacturing Practices (GMPs) which are not practical for small compounders. Manufacturers are also required to go through a lengthy Food and Drug Administration (FDA) approval process whenever they bring a new drug to market. Compounding should not be used as way to avoid GMPs and FDA approval. Because compounds are not FDA approved, they are not 'generic' forms of approved drugs. They also fall under off-label or extra-label drug use (ELDU) because they do not have FDA approved labels. This becomes important when compounding for veterinary patients which will be discussed later.

Pharmacists can play an important role in patient care through compounding. Children commonly require liquid medication when only tablets and capsules are available or require a dosage strength that isn't commercially available. Geriatric patients often have physical, emotional and social difficulties, decreasing compliance with manufactured medications and

many of their illnesses are chronic, requiring long-term therapy. Veterinary patients regularly need medications that are not available in appropriate formulations and strengths or the commercial product contains toxic excipients. Compounding is an opportunity for pharmacists to provide necessary medications in a dosage form and strength that is appropriate for each patient. Compounds account for about 10% of prescribed/ordered medications making spending on compounds $25-30 billion a year.[2]

All pharmacists are legally allowed to compound, but as compounding has become a smaller part of pharmacy over the past century, compounding education in pharmacy schools has decreased to allow room in the curriculum for more 'current' topics.[3] Therefore, simply because a person is a pharmacist does not mean that they should compound. Whether compounding for human or veterinary patients, pharmacists must be willing to invest in their education through continuing education designed to cover the practical skills as well as scientific basis for compounding.[2]

History of Compounding

Over the course of history, the definition of pharmacy has included compounding.[2] In fact, the pharmacy profession consisted only of compounding until the 20th century. At the beginning of the 20th century most drugs were still compounded, but thanks to the Industrial Revolution which was in full swing, manufacturing was on the rise. The percentage of prescriptions that were compounds steadily declined to 75% in the 1930s, 26% in the 1950s, 3-4% by 1962, and only 1% by 1973. Factors influencing the trend away from compounding included third party payers, discovery of effective medications, advertising of trade-named products, and the need to dispense more prescriptions in less time.[4]

In the 1980s and 1990s, home healthcare, total parenteral nutrition, hospice care, and pharmaceutical manufacturers decreasing the products they offered led to a resurgence of compounded medications. In 1995, 11% of prescriptions were compounds, which was a five to ten times increase over the number of compounds in the 1970s and 1980s.[4] From the mid-1990s to the mid-2000s, compounding received significant media attention, which unfortunately centered around negative stories while positive ones got very little attention. However, this time period saw the growth of compounding sections in state and national organizations as a way to help improve problems with compounding. These organizations also allotted time for compounding continuing education at their annual meetings.[5]

As compounding frequency has varied over time, so has the ~~legal~~ legislation that applies to compounding. The first applicable law was the Pure Food and Drug Act of 1906. This law was driven by the need to address food safety, and drugs were included due to the unlabeled alcohol and narcotic content. The definition of "drug" included all medications recognized in the United States Pharmacopeia (USP) or National Formulary (NF). In 1938, the Food, Drug, and Cosmetic (FD&C) Act was passed establishing the requirement for manufacturers to apply for FDA authorization before marketing new drugs. The FD&C Act has had a variety of amendments since 1938, some of which have impacted pharmacy practice.[3]

In 1996, the Animal Medicinal Drug Use Clarification Act (AMDUCA) became law. This made it legal for veterinarians to use medications off-label, which made compounding for veterinary patients legal. The act divided animals into either food animal or non-food animal based on intended use and described when off-label use would be appropriate for each group.[6] As this is still prominent in veterinary medicine, it will be discussed later.

One of the most notable compounding-related court cases occurred in 2002, when the U.S. Supreme Court decided in favor of pharmacists challenging the part of the Food and Drug Modernization Act that restricted advertising of specific compounded products. Additionally, a U.S. district court declared that the FDA had no jurisdiction over compounding practice as long as it was done in accordance with state laws and regulations.[2] The Drug Quality and Security Act (DQSA) was signed into law in November 2013. This act was designed to regulate compounding pharmacies and develop a way to track drugs from manufacturer to patient. This law was put in place after the fungal meningitis outbreak ~~due~~ which occurred due to contaminated sterile products. Since the DQSA applies primarily to sterile compounding, it will not be covered in further detail in this document.[7]

USP

The USP was started by 11 physicians meeting in the Senate Chamber of the U.S. Capitol building in 1820 to establish a pharmacopeia for the United States. Since then, USP has grown to its current mission statement, "To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods."[8]

USP is an independent body that works with the FDA as specified by U.S. law. This interaction allows FDA representatives and other government agencies to participate in Expert Committee and Expert Panel meetings. USP-NF standards are authoritative, based in science and developed by a transparent, credible process. USP-NF is recognized by the FD&C Act, which

includes USP-NF in its definition of official compendium.[2,8] This allows USP-NF standards to influence adulteration and misbranding provisions.[8] However, it is up to the state boards of pharmacy to enforce USP standards as USP itself has no enforcement powers.[2] Some states have adopted USP by reference or by including the content in their state laws; however, not all states enforce USP standards.[8]

The USP-NF contains official substance, product and preparation monographs. These monographs generally contain the following: name, definition, packaging, storage, other requirements and a specification. General chapters provide information on procedures and acceptance criteria that are commonly cited throughout the text.[8]

USP-NF is organized into four volumes and two supplements. Volume 1 contains the front matter, General Notices, General Chapters, Dietary Supplements general chapters, Reagents, and Reference Tables. Volume 2 includes USP monographs A-I, and Volume 3 contains monographs J-Z. Volume 4 contains Dietary Supplements monographs, NF Admissions/Annotations, Excipients, and NF monographs. The supplements follow a standard schedule. The First Supplement is published in February and becomes official August 1. The Second Supplement is published in June and becomes official December 1. The content from the supplements is incorporated into the new version of USP-NF each year. If the print version of USP-NF is used, the user must make sure to utilize the most current information. Alternatively, web access to USP-NF is available. The revision process for USP-NF involves a proposed revision being posted in the Pharmacopeial Forum for a 90-day comment period. At the conclusion of the comment period, the relevant USP Expert Committee reviews and incorporates the comments and approves the revision, which is then published in the next USP-NF or Supplement.[8]

USP-NF is generally broken down into chapters less than 1000 and chapters greater than 1000. Chapters less than 1000 are legally enforceable whereas chapters greater than 1000 are considered general information.[9] Chapters that apply directly to compounding include <795> Pharmaceutical Compounding – Nonsterile Preparations, <797> Pharmaceutical Compounding – Sterile Preparations, <800> Hazardous Drugs – Handling in Healthcare Settings, <1151> Pharmaceutical Dosage Forms, <1160> Pharmaceutical Calculations in Prescription Compounding, <1163> Quality Assurance in Pharmaceutical Compounding, <1176> Prescription Balances and Volumetric Apparatus, <1191> Stability Considerations in Dispensing Practice, and <1265> Written Prescription Drug Information – Guidelines.[10] USP-NF <795> directly applies to non-sterile compounding, and requirements will be discussed throughout this document.

Who Can Compound?

The pharmacist is responsible for inspecting and either approving or rejecting all steps in the compounding process. This includes components of the compound, calculations, in-process materials, containers, and labeling. The pharmacist may designate someone else such as a technician or student to perform the actual compounding of a medication, but the pharmacist is still responsible for the integrity of the compounded medication. In addition, the pharmacist should be responsible for developing/approving master formulations for compounded products.[2]

Before dispensing the medication, the pharmacist should review the formulation record and final product. Formulation record review includes verifying that appropriate ingredients, and equipment were used, calculations and measurements were performed accurately, and that the beyond-use date (BUD) is appropriate. Review of the final product should verify that the calculated and actual yields are consistent, individual dose tolerance (USP requires +/- 10%) is met, actual and expected physical characteristics are consistent, the final container is appropriate for the formulation, the product is suitably labeled including BUD and storage requirements, and documentation is appropriate.[2]

Compounding Considerations

Not every medication formulation that can be imagined is appropriate to compound. Prescribers should be using proper references to determine if a compound is appropriate. However, often these prescribers do not have the background to determine if a drug is suitable in a specific formulation. This is an area that pharmacists have been trained in and should evaluate for every compound prescription they receive. The following is a checklist that can be used to determine if a prescription is appropriate to compound. Each question represents a requirement for compounding, regardless of whether the compound is for a veterinary or human patient. With regards to a specific compound prescription, if the answer to any question is 'no', then the product should not be compounded.

Question[2]	Yes	No
Is the medication requested clinically different from commercially available products in dosage form, strength, and/or packaging? • There are no guidelines available that specify what is considered clinically different, but the prescriber should be able to clearly		

explain why a compound is required versus the approved product. • With regards to dosage it can be assumed that a dose falling within USP acceptable limits (usually +/- 10%) of the commercially available strength would not be clinically different. • Products that are duplicates of commercially available products should not be compounded.		
Is the prescription rational for the specific patient with regards to ingredients, intended use, dose, and method of administration?		
Are the physical, chemical, and therapeutic properties of each ingredient, when combined, conducive to a safe and effective medication? • Potential interactions between ingredients need to be considered. For example, combining two antibiotics together into a capsule may result in them deactivating each other prior to administration. • Route of administration must also be considered. Examples include determining if the medication is stable in the normal gastric pH range for oral formulations and evaluating if the medication will cross the skin for transdermal formulations.		
Will this compound meet the needs of the patient and achieve the desired results?		
Is there an alternative option (either commercially available or compounded) that may provide better assurances of safety and efficacy? • Compounded products do not carry the same guarantees of safety and efficacy that FDA approved products do, but published research and case reports of compounded products provide more assurance than compounds with no available literature.		
Is there a valid prescriber-pharmacist-patient relationship?		
Can appropriate ingredients be obtained with assured identity, quality and purity? • Approved products or USP-NF quality powders are the preferred sources for active ingredients. • Regardless of where products are obtained from, they should have a Certificate of Analysis (CoA) and if the product is USP-NF then it should meet those specifications.		
Does the pharmacist have the training and knowledge necessary to prepare the compound?		
Is the necessary equipment available and in working order?		
Is there available information on use, preparation, stability, administration,		

storage, and BUD determination for the compound? • Unless there are studies indicating stability for the exact compound formulation, then USP beyond-use dating guidelines should be used.		
Are appropriate standard operating procedures (SOPs) in place for compounding with regards to documentation, quality control checks, investigating and correcting failures?		
Is the prescribed quantity appropriate based on the BUD? • The patient should not be provided with more medication than they will reasonably use by the BUD.		

Ingredient Selection

According to USP <795>, "the pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official standards, and relevant scientific data and information".[10] The old saying, 'garbage in, garbage out' applies here. Compounded products can't provide the assurances that approved products do, but the quality of the product will be much more reliable if high quality ingredients are used. Ingredient grades include USP/NF, American Chemical Society (ACS) reagent, chemically pure (CP), and technical or commercial. USP/NF is the desired grade as it meets the minimum purity standards and conforms to all requirements set by USP/NF. ACS reagent grade is high purity and meets the specifications set by the Reagent Chemicals Committee of the ACS. CP is more refined than technical or commercial but the quality is unknown. Technical or commercial grade is considered intermediate in quality. In human compounding either bulk powders or manufactured products can be used as the source of the active ingredient. However, in veterinary compounding, commercially available products are required with a few exceptions. The problem with using manufactured products is that they are allowed a tolerance range (usually +/- 10%), which can compromise the strength of the compound, taking it out of the allowed +/- 10% for the final product. The additional excipients in manufactured products can also pose problems with patient allergies as well as certain formulations such as solutions and transdermal products. Other problems with using commercially available products include higher cost, effects of excipients on safety, efficacy and stability, pH effects, and the quantity of commercial product necessary to achieve desired strength.[2]

In addition to selecting high quality ingredients, it is important to know the characteristics of the powder. For example, hygroscopic and deliquescent powders will absorb water from the air. Therefore, weighing should be done quickly after opening the container. If the powder is

weighed and allowed to sit it may weigh more if re-weighed at a later time. Another important consideration is whether or not the drug is in salt form. The purpose of the salt form is usually to increase the solubility of the drug. Some drugs are dosed based on their salt forms and some are based only on the drug itself. For example, Ceftin tablets contain 250 or 500mg of cefuroxime as cefuroxime axetil. When compounding with the commercial tablets this isn't an issue; however, if bulk cefuroxime powder is used it is important to use the correct amount to obtain the cefuroxime necessary. It is the responsibility of the pharmacist to make sure the quantity of drug needed is calculated correctly.[2]

Flavoring Compounds

Flavoring provides a way to increase compliance for both children and pets. However, taste is not the only concern with flavor. Smell and color can also affect the flavor experience with most people being more sensitive to odors than taste. Generally flavoring is added to be about 1-3% of the final volume.[2] If a liquid is over-flavored, it will not have an appealing taste.

Different drugs will have different inherent flavors and odors. Flavoring will be most effective if it is done to correlate with the drug's natural characteristics. For example, if a drug is bitter, an acceptable bitter flavor such as chocolate can be used or a citrus flavor can be added to a drug with a natural sour flavor. A drug's taste and odor can be predicted based on its chemical structure. The following table summarizes the chemical characteristics and their effect on flavor.[2]

Taste	Chemical Property
Bitter	High molecular weight salts
Sour	H^+
Salty	Presence of both anions and cations
Sharp	Unsaturation
Sweet	Polyhydroxyl compounds, polyhydrogenated compounds, alpha-amino acids
Odor	**Chemical Property**
Camphoraceous	Tertiary carbon atom
Fruity	Esters, lactones
Pleasant	Ketones

Not all drugs and flavors are compatible. Flavorings are made up of many chemicals regardless of whether they are natural or artificial. Flavors can adsorb to containers and sorb to suspended materials. If a compounded medication loses its flavor, this should be investigated.[2]

Beyond-Use Dating

Manufactured products have an expiration date, which is the time at which the drug has degraded to the point of being outside of acceptability limits. This date is determined through thorough testing by the manufacturer. However, compounded products have BUDs which indicate the date which the product should not be used after. Unlike manufactured products these dates are often conservative estimates of the product's stability. USP-NF defines stability as "the extent to which a dosage form retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its preparation."[10] Stability is complicated to determine as it encompasses the nature of the drug and its degradation kinetics, the container the formulation is packaged in, the expected storage conditions, use of preservatives or stabilizers, dosage form, route of administration, and scientific, laboratory, or reference data. Word of mouth should not be used for determining BUDs.[2] USP-NF provides guidelines for beyond-use dating. These timeframes should be used unless there is formulation specific stability data indicating a longer BUD is appropriate.

The following table provides BUDs as indicated in USP-NF <795>.

Formulation	BUD
Non-aqueous formulation • Oil-based suspensions • Capsules	Not later than the time remaining until the earliest expiration date of any active ingredient or **6 months**, whichever is earlier.
Water-containing oral formulation • Aqueous suspension	Not later than **14 days** under refrigeration.
Water-containing topical/dermal and mucosal liquid and semisolid formulations • Aqueous otic preparation • Topical gel	Not later than **30 days**.

However, the BUD date should never extend beyond the expiration dates of the ingredients.[10]

Quality Control

A quality control program should verify that a product is compounded correctly and that the BUD is appropriate. Chemical and analytical testing is necessary and can be done in-house or outsourced. The nature and scope of appropriate chemical and analytical quality control will not be covered here. This paper will focus on physical tests that should be conducted in all compounding pharmacies.[2]

Physical tests are used to verify the uniformity and accuracy of compounded preparations. The table below summarizes which physical tests are appropriate for the dosage forms discussed in this paper.[2] The pharmacist should perform or verify the results of these tests.

Dosage Form	Individual Weights	Average Individual Weights	Total Preparation Weight	pH	Physical Observation
Capsules	x	x	x		x
Solutions/Suspensions				x	x

Record Keeping

Compounding records are a characteristic of a high-quality compounding pharmacy, and they are required by state boards of pharmacy. These records include SOPs, formulation records, compounding records, material safety data sheets (MSDS) and CoAs. SOPs provide detailed instructions for training, equipment maintenance, inventory, and compounding processes. These should be reviewed and updated regularly. Formulation records are the 'recipes' for compounding. They provide all information necessary to reproduce a preparation such as name, strength, and dosage form, ingredients and their quantities, necessary equipment, relevant calculations, mixing instructions, quality control measures, BUD, container for final preparation, storage requirements and references for the information such as stability studies. The compounding record is the documentation of what was actually done. The formulation used should be referenced and the compounding record should contain the following:

- Quantity prepared
- Ingredients used (including their lot numbers, manufacturers, and expiration dates)
- Date of compounding
- Assigned internal lot number
- Prescription number
- BUD
- Quality control results
- Signature of person compounding and approving pharmacist

MSDS are required for all drug substances. These should be easily accessible to everyone working with these chemicals. CoAs should be checked for each lot of drug powder that is received. These are not necessary for approved products. The CoA should be kept on hand (either hard copy or electronically) for the duration of therapy with the product the drug was used to compound.[2]

Veterinary Compounding

With the wide variety of species and the size variety within each species, compounding is an important part of veterinary medicine. Although vets are legally allowed to compound and dispense their own medications, they often prescribe compounds for pharmacists that have more knowledge and experience with compounding to fill. Veterinary compounding has many similarities to human compounding. It is important to look at compounds with considerations for what is best for the patient. In the most basic sense, this would include what dosage form is most ideal for the patient, what flavor would be most appropriate, are there any ingredients

that may be toxic to the patient, and what legal implications are there. Along the lines of legal concerns, it is important to consider the purpose of the animal. If the animal is being used in competitions or for human consumption, then predictability of drug elimination is important.

Common compounded veterinary dosage forms include capsules, oral liquids and transdermal gels. Capsules are commonly used in dogs and cats, but some owners may find liquids easier to administer. In other species such as birds and ferrets, liquid medications are preferred. Since a majority of cats are reluctant to take medication the transdermal route is becoming more popular. However, there is a lack of data concerning efficacy and safety of transdermal products as well as a number of medications that are not appropriate for transdermal administration due to risk to the owner or pet.[11] The compounder, veterinarian, and pet owner should work together to determine the best dosage route based on efficacy, safety, and patient acceptability.

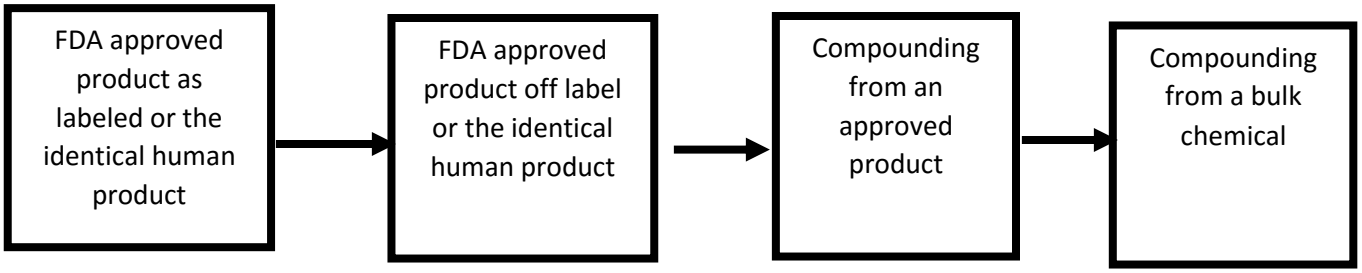
Flavoring can be an easy way to make oral medications more palatable for veterinary patients. There are a wide variety of flavors in both aqueous and oil-miscible forms designed for veterinary patients, such as beef, liver, chicken, and fish flavors. Empty capsules with flavors such as chicken and bacon are also available for compounding. While the above listed flavors may be obvious choices for most cats and dogs, these aren't appropriate for all veterinary species. For example, horses and ferrets often prefer sweet flavors.[12] As most pets receiving compounded medications are considered members of the family, the best way to choose a flavor is by consulting with the owner, who will likely know if their animal fits the flavor stereotype for that species or if they would prefer something more unusual. For example, a cat may prefer marshmallow flavoring instead of fish.

Toxic ingredients can be a reason to compound a suspension instead of using the commercially available solution, as is the case with gabapentin solution which contains xylitol. It is important for the compounding pharmacist to be aware of foods and pharmaceutical ingredients that are toxic to the species for which they are compounding. Consider a scenario in which a suspension needs flavored for a dog. Even if the dog likes the taste of chocolate, the medication should not be flavored that way. Although the flavoring likely won't be toxic, the dog may develop a desire to seek out chocolate, leading to a toxic ingestion. Listing veterinary toxicities goes beyond the scope of this document, but additional information can be found at www.petpoisoncontrol.com.

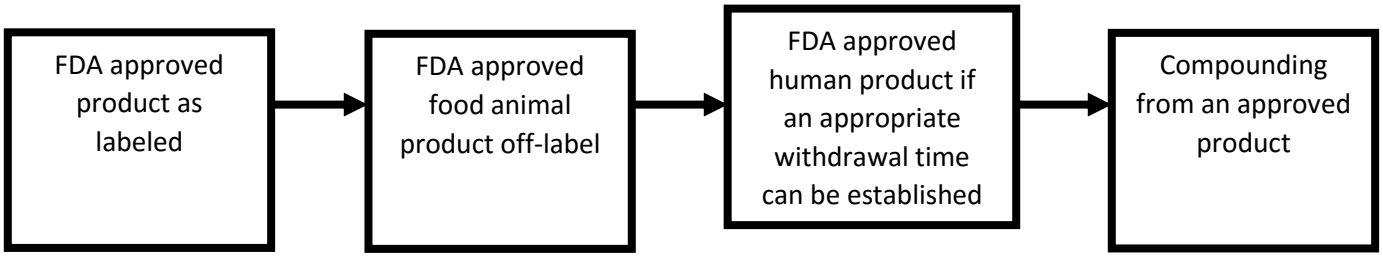
The area where veterinary compounding most differs from human compounding is the legal side. Veterinary patients are split into two general groups – food animal and non-food animal.

Which group a particular animal falls into is based on its intended use, not its species. With food animals there is concern about drug residues ending up in the human food supply. The safety of the human food supply is the driving factor for a number of compounding legal considerations. One of the most notable laws is AMDUCA. This act established criteria for ELDU in veterinary patients. Since compounded products are not FDA approved, they are always extra-label which places them under ELDU requirements. While AMDUCA addressed compounding using approved products for the base, it did not address compounding from bulk chemicals. Opinions on whether using bulk chemicals as the drug source in compounding is legal have changed over time through various FDA guidance documents. However, there have not been any laws addressing this. The currently accepted algorithms for compounding in veterinary patients are below.[6]

Non-Food Animal ELDU Algorithm:[6]



Food Animal ELDU Algorithm:[6]



The above algorithms should be followed from left to right, and only if the option to the left is not possible should the option on the right be considered. For example, a cat needs methimazole. There are commercially available tablets, in an appropriate strength, but the owner is unable to administer oral medications. Cats are not used as food in the U.S. so the non-food animal algorithm will be followed. The first option is an FDA approved product as labeled or the identical human product. Since only tablets are approved, and this route of administration doesn't work, this is not feasible. This also prevents the second option. Next compounding can be considered. Methimazole transdermal has studies showing safety and

efficacy and would be a good option for this cat. However, transdermal products should only be prepared from bulk chemicals because the extra excipients in the commercially available tablets may prevent drug absorption across the skin. Therefore, compounding transdermal methimazole using bulk chemical would be appropriate for a cat for which an oral product is not feasible.

AMDUCA also includes a list of drugs that are not allowed to be used in an extra-label manner in food animals.[6] Since compounding is always ELDU, these medications can never be compounded. The current list of medications prohibited from ELDU in food animals is available from the Food Animal Residue Avoidance Databank (FARAD) at http://www.farad.org/eldu/prohibit.asp. In addition to food animal legal concerns, the prudent compounder will also determine if the animal is being used for competition purposes. For example, horses are often used for competitive events, and depending on the breed and the nature of competition, different drug use laws are in play. These laws are set by the Racing Commission in each state, the United States Equestrian Federation (USEF), Fédération Equestre Internationale (FEI), and other equestrian organizations. These drug rules state the time that must elapse between drug administration and competition as determined based on commercial products. Any variability in pharmacokinetics with compounded products must be accounted for if the horse will be competing.

Specific Dosage Forms

Capsules

Capsules are one of the most popular dosage forms due to ease of compounding, versatility, and ability to mask taste. Capsules are either soft-gelatin or hard-gelatin with the hard-gelatin allowing either rapid or sustained release. The first capsule was invented in 1833, and capsules were included in USP for the first time with the 12th revision. Capsules are portable, light weight, and come in many different colors, making them a popular dosage form. However, capsules are not appropriate for readily soluble drugs (i.e. salts) because the salts rapidly dissolve, creating a concentrated drug solution leading to nausea and vomiting.[2] In addition to traditional capsules, compounded capsules can be sustained-release or contain liquids. However, only traditional powder capsules will be discussed here.

Capsules generally consist of an active drug powder and a “filler” such as lactose. The active drug powder can come from a commercially available product such as a tablet or capsule. However, care needs to be taken to make sure that the particle sizes of each ingredient are

approximately the same size to allow even distribution from one capsule to the next. Once the powders are weighed out and within the same particle size range, they can be mixed using a variety of methods. However, regardless of mixing method, the end result needs to be a homogenous mixture. Since a majority of drug powders as well as the common fillers are white, use of a "tracer" is one method to verify the active drug is distributed evenly throughout the powder. This involves mixing the active drug with a coloring powder so that the drug is evenly colored. Then the filler can be mixed in with the goal of obtaining a uniformly colored mixture. If the powders are light and fluffy making them difficult to work with, adding a couple drops of either alcohol, mineral oil or water can be helpful.[2] Once the powders are mixed, capsules can be prepared by either hand-packing or using a "capsule machine".

The patient should be a major consideration when selecting a capsule size. Capsules for human use range in size from No. 5 which is the smallest to No. 000 which is the largest. The number does not indicate the capacity of the capsule, just its capacity relative to other capsules. Although human capsules are commonly used for veterinary patients, veterinary capsules come in sizes No. 10 (1 oz.), No. 11 (1/2 oz.), and No. 12 (1/4 oz.), but these are not commonly used. Flavored capsules are available in common sizes as well to further improve compliance, especially for veterinary patients. Generally, capsules can hold anywhere from 65 to 1000mg of powder. However, the first consideration should be what size capsule would work best for the patient. Small capsules (i.e. No. 4 and No.5) can be difficult for some patients to handle while capsules larger than No. 1 can be difficult for some patients to swallow.[2] With veterinary patients, the size of the patient should be taken into consideration. For small dogs and cats, No. 3 capsules are usually acceptable, while large dogs can often take No. 1 or No. 0 without a problem. Once the preferred size range for a patient is determined, then powder volume should be considered. If the capsule is larger than the amount of drug required, then filler can be added. If the capsule is too small to fit the entire amount of active drug, then the dose can be split over multiple capsules.[2] Although changing prescription directions from taking one capsule to two capsules requires approval from the prescriber, it is a way in which compounding pharmacists can improve patient compliance.

Capsules can also be used to combine multiple medications and decrease a patient's "pill burden". However, this should be undertaken with caution. Even with dry powders drug interactions can occur that can cause stability to decrease to the point where it shortens the BUD or the medication is ineffective when it reaches the patient. If drug incompatibility is a problem, but the patient needs their medications combined, a small capsule containing one medication can be placed inside a larger capsule containing the other medication. This allows the patient to only take one capsule, but prevents the incompatibility.[2]

Solutions/Suspensions

Oral liquids have a wide range of applications in patient care. Liquids allow for individualized doses and are often easier to administer to children and veterinary patients. Other benefits of liquid medications include a more convenient route of administration for large quantities of medication, and drugs may be more bioavailable in liquid form or at least absorbed quicker.[2] However, many medications are only available in tablet or capsule form.

Liquid dosage forms can go by a variety of different names depending on their exact structure. However, the most common ones are solutions and suspensions. Solutions are liquid formulations containing at least one drug dispersed in an appropriate solvent. In a solution, the drug has been molecularly dispersed preventing drug settling. This requires an appropriate solvent based on the characteristics of the drug. In general, "like dissolves like". Therefore, polar drugs will usually dissolve in polar solvents and nonpolar drugs will usually dissolve in nonpolar solvents. However, this is challenging because many drugs have intermediate polarity.[2] Flavoring, coloring, and sweeteners can be added to improve palatability; however, it is important to verify that these are appropriate based on the composition of the solution. For example, if an aqueous suspension is prepared, then aqueous flavoring should be used.

While solutions can be beneficial, they have inherent difficulties. The molecular dispersion that takes place in solutions can make already unstable drugs more unstable. Solutions are made by dissolving a drug in an appropriate solvent. Often times stirring is sufficient to dissolve the drug, but sometimes heat or agitation, such as with a vortex may be required. Although heat can be helpful to solubilize a drug, it can also cause negative effects on the drug, which the compounder must take into consideration. When preparing solutions, the compounder should consider both the physical and chemical properties, order of mixing, techniques required for compounding, ingredient incompatibilities, stability over time, and necessary accessory labels. General considerations for incorporating a drug into solution include the following:[2]

- Small particles dissolve faster than large particles.
- Stirring increases the rate at which a drug will solubilize.
- Drugs that are more soluble will dissolve faster.
- The more viscous the liquid, the less drug that will be dissolved.
- As temperature increases, drug solubility generally increases.
- For bases, as the pH is decreased, the solubility increases.
- For acids, as the pH is increased, the solubility increases.

Suspensions are created when the drug is not soluble in an appropriate vehicle. Oral suspensions consist of a finely divided solid dispersed throughout a liquid also known as the suspending agent or vehicle. Ideally this suspending agent will be viscous enough to prevent the drug from settling out of suspension while still being easy to pour. Since larger particles settle out of suspension quicker than small particles, the drug should be prepared as small particles that are approximately the same size. Before incorporating the powder into the liquid, it should be thoroughly wetted with an appropriate wetting agent. The minimal amount of wetting agent to produce a paste-like consistency should be used. This will help with dispersing the drug throughout the vehicle. Despite an appropriate vehicle and wetting the powder, drug will still settle out of suspension, so all patients should be counseled to shake the suspension before each dose. Therefore, containers should have sufficient headspace to allow for shaking.[2]

When dispensing liquid compounds, patients should be counseled on signs of instability. For solutions these include clarity, precipitation, odor, loss of volume, and mold or bacterial growth. For suspensions, signs of instability include difficulty re-suspending the drug, odor, loss of volume, and mold or bacterial growth.[2]

Conclusion

Compounding is an important part of pharmacy practice. It helps improve patient care while requiring the pharmacist to use their drug knowledge, chemistry background, and drug information skills to prepare compounds that are as safe and effective as possible. However, compounds do not contain the assurances that FDA approved products do, increasing the risk of errors. Therefore, pharmacists that compound for any population need to continually stay up-to-date on compounding techniques and concerns.

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ACTIVITY TEST

1. **Which of the following identifies the major differences between compounding and manufacturing?**
    a. Compounding is patient-specific whereas manufacturing is performed on a large scale
    b. Compounding is creating generic medications whereas manufacturing applies to brand name medications
    c. Compounding and manufacturing are very similar and differ only in that a pharmacist compounds and a PhD manufactures
    d. Compounding refers to preparing medications for veterinary patients and manufacturing is preparing medications for human patients

2. **Which of the following laws is correctly matched with its effect on pharmacy?**
    a. Pure Food and Drug Act – Established to address safety of food and drugs
    b. Food, Drug, and Cosmetic (FD&C) Act – Established the requirement for manufacturers to apply for FDA authorization before marketing new drugs
    c. Animal Medicinal Drug Use Clarification Act (AMDUCA) – Made it legal for veterinarians to use medications off-label
    d. All of the above

3. **Which of the following is the current USP mission statement?**
    a. To improve non-sterile compounding by ensuring the quality, safety, and benefit of compound products
    b. To improve drug quality by ensuring the quality, safety, and benefit of manufactured products
    c. To improve public health by increasing availability of medications through large-scale compounding
    d. To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods

4. **What organization is responsible for enforcing USP standards?**
    a. USP is an enforcement body and therefore responsible for enforcement of its standards
    b. USP is a subset of the FDA and therefore FDA is responsible for its enforcement
    c. It is up to the state boards of pharmacy to enforce USP standards
    d. USP only provides suggestions and therefore is not enforceable

5. **Which of the following records kept by a compounding pharmacy is correctly matched with its purpose?**
    a. **CoAs: contain safety information for all products used in compounding**
    b. **SOPs: detailed instructions for training, equipment maintenance, inventory, and compounding processes**
    c. **Formulation records: The documentation of what was really done when compounding**
    d. **Compounding records: 'Recipes' for compounding**

6. **Which of the following is contained within USP-NF?**
    a. **Official substance monographs**
    b. **Official product monographs**
    c. **Official preparation monographs**
    d. **All of the above**

7. **Which of the following USP chapters are considered "enforceable"?**
    a. **Chapters numbered less than 1000**
    b. **Chapters numbered greater than 1000**
    c. **All chapters**
    d. **USP is not enforceable**

8. **Which of the following factors led to the decrease in compounding from 1930-1980?**
    a. **Advertising of trade name products**
    b. **Time constraints**
    c. **Third-party payers**
    d. **All of the above**

9. **Case for questions 9-11:**
    MJ is an elderly woman who is currently taking metoprolol BID, Lisinopril QD, furosemide BID, and spironolactone BID for her heart failure. She is having difficulty keeping all of these medications straight and is asking you (a compounding pharmacist) if there is any way she can just get one medication to take instead of keeping track of all of these. Your first thought is a combination capsule containing all of the necessary medications.

Which of the following areas of concern should be considered prior or agreeing to compound the medication?

a. Capsule size that would work best for the patient
b. Potential interactions between the medications if they are all within the same capsule
c. Size of the capsule necessary to hold the medications
d. All of the above

10. Who is responsible for developing the master formulation for this patient's combination capsule?

a. The patient
b. The pharmacist
c. A pharmacy technician
d. The pharmacy manager

11. What would be the longest appropriate BUD for these capsules?

a. 14 days
b. 30 days
c. 180 days
d. 1 year

12. A patient brings a prescription for 98mg doxycycline capsules to your compounding pharmacy. What would be the correct course of action?

a. Compound this medication and give it a 180-day BUD as doxycycline is not commercially available in 100mg capsules
b. Contact the prescriber and explain that capsules are only good for 2 weeks so the patient should only receive a 2-week quantity
c. Contact the prescriber and explain that doxycycline 100mg capsules are commercially available and ask if there is a specific reason as to why the patient is not able to receive the commercially available product
d. Compound a 98mg/mL suspension based on the patient's requests. There is no need to contact the prescriber

13. When preparing a compounded aqueous suspension, what BUD should be assigned based on USP criteria?

a. 14 days at room temperature
b. 14 days refrigerated
c. 30 days refrigerated
d. 180 days at room temperature

14. **Which ingredient grade is the first choice when using bulk chemicals to compound?**
    a. ACS reagent
    b. Chemically pure (CP)
    c. USP/NF
    d. Technical

15. **Which physical tests should be performed for quality control on a suspension?**
    a. Individual weights, pH
    b. Individual weights, pH, physical observation
    c. pH, physical observation
    d. total preparation weight

16. **Which of the following are possible concerns with using manufactured products as the base for a compound?**
    a. They are all allowed a tolerance rage, compromising the strength of the compound
    b. Additional excipients can pose problems with patient allergies or certain formulations
    c. Effects of excipients on stability of the compound
    d. All of the above

17. **Which type of medication would NOT be appropriate for compounding into capsules?**
    a. Salt forms of drugs
    b. Light and fluffy powders
    c. Medications needed in small quantities
    d. All of the above

18. **A competitive jumping horse is in need of doxycycline 5g BID. Doxycycline is commercially available as 100mg capsules. The vet called into your compounding pharmacy asking about administration options. Which of the following should be considered before answering the vet's question?**
    a. Most ideal dosage form
    b. Legal implications
    c. Appropriate flavoring
    d. All of the above

19. Which of the following describes the appropriate analysis of this request?

a. The commercially available capsules are the most appropriate dosage form for this horse
b. This horse is likely a food animal and therefore, this product should not be compounded
c. Apple may be an appropriate flavor but the owner can be consulted for the best flavor for this horse
d. All of the above

20. Which law provides guidelines that can be used to determine if compounding is appropriate for this horse?

a. AMDUCA
b. DQSA
c. FD&C
d. USP

Please submit your final responses on freeCE.com. Thank you.