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Compounding Regulations

A quick search of the news will provide a variety of historical cases in both human and veterinary medicine where poor-quality compounds resulted in significant morbidity and mortality. In these cases, it is often argued that something was not done legally, and if all relevant laws had been followed, the compounds would not have been made. Therefore, it behooves anyone preparing compounded medications to be well aware of the regulations surrounding compounding.

Clenbuterol Toxicosis in Three Horses in 2006 [1–3]: Three horses displayed toxicity symptoms between 12 and 24 h after receiving a clenbuterol compound that contained 70-fold the amount of clenbuterol indicated on the labeling. The label indicated that the product contained 72.5 mcg/ml of clenbuterol when it actually contained 5 mg/ml. The commercial product containing clenbuterol at 72 mcg/ml had previously been used in at least one of the horses without issue. Two of the three horses were euthanized due to complications. The illegal "compounded" product was obtained from an unidentified source and administered without a prescription.

Twenty-one Polo Ponies Die Due to Compounding Error in 2009 [4, 5]: Twenty-one polo ponies competing at the US Open Polo Championship in 2009 collapsed with most dying within hours due to a selenium overdose. Franck's Pharmacy in Ocala, FL had made an error when compounding a vitamin mixture containing B-12, selenium, and other minerals, which resulted in 100 times more selenium than intended. It was determined that the horses had 10–15 times more selenium in their blood and 10–20 times more in their liver than the normal amount, which led to their deaths. The prescribed compound was intended to mimic Biodyl, which is used commonly in Europe, Asia, and Latin America. However, Biodyl is not a Food and Drug Administration (FDA)–approved product.

Fungal Meningitis Outbreak in 2012–2013 [6–8]: Three lots of a contaminated preservative-free methylprednisolone acetate injection compounded by the New England Compounding Center (NECC) in Framingham, MA were responsible for 778 fungal infections resulting in 76

Drug Compounding for Veterinary Professionals, First Edition. Lauren R. Eichstadt Forsythe and Alexandria E. Gochenauer.

Companion Website: www.wiley.com/go/forsythe/drug

deaths across 20 states. The three lots included more than 17000 vials of the medication which were improperly sterilized through a nonverified sterilization process and improperly tested to ensure sterility prior to being shipped throughout the United States.

Upon investigation of the compounding facility, it was noted that drugs were routinely shipped before sterility testing results were received, compounds were prepared utilizing expired ingredients, and cleaning logs were ignored as was the presence of mold and bacteria in the clean rooms. Additionally, the NECC was attempting to conceal that a technician whose license had been revoked by the Massachusetts Board of Pharmacy (BOP) was responsible for compounding sterile products.

Compounded Equine Protozoal Myeloencephalitis (EPM) Drug Linked to Equine Deaths in 2014 [9, 10]: Ten horses (eight in Florida and two in Kentucky) experienced adverse effects including seizures and fever with four horses dying after receiving a compounded EPM medication. A toltrazuril/pyrimethamine product was compounded as a paste and suspension by Wickliffe Veterinary Pharmacy of Lexington, KY containing more pyrimethamine than indicated on the labeling. Typically, the compounded paste contains 416-mg/ml toltrazuril and 17-mg/ml pyrimethamine. The lawsuit states that when the implicated product was tested, it actually contained 22 mg/ml of toltrazuril and 229 mg/ml of pyrimethamine.

Compounded EPM Drug Linked to Equine Deaths in 2019 [11, 12]: One lot of a compounded paste labeled to contain 416-mg/ml toltrazuril and 17-mg/ml pyrimethamine and compounded by Rapid Equine Solutions in Aston, PA was found to contain 18–21 times the labeled pyrimethamine concentration. The product was recalled and tested after adverse effects followed by death were noted in at least three horses. Specifically, the affected lot was found to contain 13.5 and 11.2 mg/ml of toltrazuril (3% of the labeled concentration) and 361 and 307 mg/ml of pyrimethamine (2122 and 1808% of the labeled concentration) in the two separate samples that were tested by the FDA.

However, veterinary compounding regulations are not always black and white. Common causes of confusion include the following:

- Regulations may not clearly address practical concerns.
- Human compounding regulations are often unclear whether they apply to veterinary compounding.
- Federal regulations that exempt animal patients on the federal level may be applied to animal patients at the state level.
- Compounding is largely regulated by the states resulting in significant state-to-state variation.
- Guidance for Industry (GFI) and Compliance Policy Guides (CPG) do not have the force of law but are often given significant weight.
- The regulatory landscape surrounding veterinary compounding is continuously changing and evolving to address problems and concerns that arise.
- What qualifies as compounding varies depending on which definition is being referenced.

Due to wide state-to-state variation, and regulations and standards that frequently change, this chapter is only designed to provide an overview and a starting point for further research into regulations applicable to your practice.

Organizations and Regulatory Agencies Involved with Compounding

Compounding regulations fall under a variety of agencies including:

- Food and Drug Administration
- United States Pharmacopeia (USP)
- Drug Enforcement Administration (DEA)
- State Boards of Pharmacy
- State Veterinary Boards

Food and Drug Administration

The FDA is an agency with an overall mission to "protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation …" [13]. It is further divided into nine centers, which includes the Center for Veterinary Medicine, which has a mission of "protecting human and animal health." The FDA is responsible for drug approval in the United States. Compounded drugs are not approved products, but the FDA maintains oversight through compounding regulations. However, patient-specific compounding is largely turfed to the states to regulate. Potentially, the FDA could conduct inspections, issue warning letters, and take additional actions such as injunctions, seizures, and criminal prosecution. Practically, the FDA only inspects compounding pharmacies on a "for cause" basis. Limiting factors that prevent the FDA from conducting regular inspections of compounding pharmacies include a lack of a comprehensive list of all compounding pharmacies because there is no requirement to register with the FDA, and a lack of resources to inspect the thousands of compounding pharmacies and veterinarians [14].

The FDA does complete a handful of compounding pharmacy inspections each year based on reports of adverse effects or illegal compounding. Between 2003 and 2015, the FDA conducted 39 inspections. Two reasons for warning letters issued by the FDA include large-scale compounding from bulk chemicals and compounding without a documented medical need. As a result of these inspections, multiple legal cases over the past two decades have challenged the FDA's oversight of compounded medications demonstrating that the exact role of the FDA in regulating compounded medications for nonfood animals remains unclear [14].

United States Pharmacopeia

The USP is an independent, nonprofit organization established in 1820 by a group of physicians. The physicians had noticed that ordering the same compounded medication from different apothecaries produced very different efficacy and safety. The initial intent of the USP was to standardize the quality of compounded medications. The USP evolved over the years to incorporate representatives from many different professions and to adjust to new advances such as the transition from using primarily compounded medications to manufactured medications being the predominant medication source. USP's mission statement is "To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods" [15].

The USP is not a government agency. Instead, it operates as a standard setting body that works with FDA representatives and other government agencies. USP-NF is two compendia: the USP and the National Formulary (NF). Standards that are included in the USP-NF are based in science and

developed through a transparent process that seeks stakeholder input. Active drugs that meet the USP standards are indicated with "USP" following the drug name (e.g. methimazole, USP). Compounding excipients that meet the USP standards are indicated with "NF" following the excipient name (e.g. Simple Syrup, NF). Since the USP is not a regulatory body, it does not enforce its standards. USP-NF is recognized in the Food, Drug, and Cosmetic (FD&C) Act as an official compendium, which connects USP standards with adulterating and misbranding provisions. However, the compounding standards are largely enforced by state Boards of Pharmacy. Some states incorporate USP standards into their state regulations by reference, and others may include the content with their own edits resulting in compounding regulations that vary throughout the country. While it is currently unclear and state specific whether USP standards apply to and/or are enforced for veterinarians compounding in their practices, they do clearly apply to pharmacies that compound for veterinary patients in all states.

A new version of USP-NF is published yearly with two supplements each year. The first supplement is published in February and becomes official on August 1, and the second supplement is published in June and becomes official on December 1. The content from the previous year's supplements is incorporated into each new version. The USP-NF contains chapters numbered less than 1000, which are legally enforceable, and chapters numbered greater than 1000, which are considered general information.

USP-NF provides standards for drugs (including dosage forms and compounded medications), excipients, biologics, dietary supplements, and medical devices. From the compounding aspect, there are three main chapters, USP <795> Pharmaceutical Compounding – Nonsterile Preparations, USP <797> Pharmaceutical Compounding – Sterile Preparations, and USP <800> Hazardous Drugs – Handling in Healthcare Settings. However, there are also several supporting chapters that provide additional information and requirements on topics including, but not limited to, sterility testing, quality assurance, balances and volumetric apparatus, and compounding for drug studies. USP chapters are written by expert committees made up of experts from a variety of fields relevant to the topic of the chapter. A brief summary of what each of the three main chapters mentioned above include follows. However, the exact requirements will not be discussed in this section due to their changing nature. It is expected that anyone compounding will review the relevant chapters prior to compounding and refer to them frequently.

USP Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations is the chapter that outlines minimum standards for preparing nonsterile compounds. Examples of nonsterile compounds include, but are not limited to, oral liquids, topical creams, and otic medications. Topics covered include training and evaluation of those compounding, hygiene and garbing requirements, compounding facilities, cleaning and sanitizing requirements, equipment considerations, formulation considerations, compounding records and documentation, quality assurance/quality control, labeling, establishing beyond-use dates, and standard operating procedures (SOPs) as they relate to nonsterile compounding.

USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations is the chapter that outlines minimum standards for preparing sterile compounds. Examples of sterile compounds include, but are not limited to, injectable medications (intramuscular, subcutaneous, and intravenous [IV]) and ophthalmic preparations. Topics covered include training and evaluation of those compounding, hygiene and garbing, compounding facilities and equipment, equipment certification and recertification, air and surface monitoring for microbiological contamination, cleaning and disinfecting, sterilization, formulation considerations, compounding documentation and records, quality assurance/quality control, labeling, beyond-use dates, and SOPs as they relate to sterile compounding.

While USP chapters <795> and <797> focus on the quality of the compound, which relates to the safety of the patient, USP Chapter <800> Hazardous Drugs – Handling in Healthcare Settings focuses on the safety of the compounder while preparing the medication. USP <800> applies to both sterile and nonsterile compounding of hazardous medications. The National Institute for Occupational Safety and Health (NIOSH) publishes a list of hazardous drugs titled NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. This list includes different groups of hazardous drugs, and USP <800> references this list when determining if a drug is considered hazardous. However, it is important to note that USP <800> requires compounders to evaluate medications new to market since the list was last published and other drugs not considered for inclusion (i.e. veterinary-only drugs) to determine if they appear to meet the NIOSH definition of hazardous. Potential points to evaluate include drug class, drug structure, and warnings provided on the manufacturer's labeling. USP <800> includes topics such as types of exposure, responsibilities for those handling hazardous drugs, facility and engineering controls, environmental evaluations, personal protective equipment, training, hazard communication, spill control, documentation, SOPs, and handling requirements from drug receipt to administration.

Compounded Preparation Monographs present formulations used in human and/or veterinary patients. These monographs provide a specific formula including ingredients and quantities, directions to prepare the compound, a maximum beyond-use date determined by stability studies, storage and packaging information, acceptable pH ranges, and stability-indicating assays. Compounded Preparation Monographs have been included in the USP since 1820. A list of currently available monographs as well as failed studies can be found at www.usp.org. Using a compounded preparation monograph from the USP is a reliable way to make sure that a compound is being prepared in accordance with necessary stability data and formulation considerations. There are dozens of veterinary-specific monographs as well as about 200 nonveterinary specific monographs, many of which can be used for veterinary patients [16].

The USP Compounding Compendium is a collection of USP chapters and monographs that are applicable to compounding. In addition to general chapters <795>, <797>, and <800>, the Compounding Compendium includes the following general chapters:

- <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging
- <1160> Pharmaceutical Calculations in Prescription Compounding
- <1163> Quality Assurance in Pharmaceutical Compounding
- <1168> Compounding for Phase I Investigational Studies
- <1176> Prescription Balances and Volumetric Apparatus

The Compendium also includes the supporting general chapters that are referenced in the compounding-specific chapters listed above.

Drug Enforcement Administration

The DEA's mission is "to enforce the controlled substance laws and regulations of the United States and bring to the criminal and civil justice system of the United States, or any other competent jurisdiction, those organizations and principal members of organizations, involved in the growing, manufacture, or distribution of controlled substances appearing in or destined for illicit traffic in the United States; and to recommend and support nonenforcement programs aimed at reducing the availability of illicit controlled substances on the domestic and international markets" [17]. Based on this mission, the DEA is concerned with compounding that involves controlled substances, but they are not involved in compounding of noncontrolled substances. Practically,

DEA compliance with regards to compounding involves following all controlled substance regulations when preparing compounded medications utilizing controlled substances.

State Boards of Pharmacy

State Boards of Pharmacy are responsible for overseeing the practice of pharmacy within their state, which includes compounding done by those licensed under the BOP such as pharmacists and pharmacy technicians. Pharmacy boards also require out-of-state pharmacies to be licensed for each state they are shipping to. This allows the pharmacy board to hold out-of-state pharmacies to the same standards as those located within the state. This becomes significant with compounded medications because states may have vastly different requirements for compounding pharmacies with regard to licensure and inspection. Depending on the way a state is set up, the pharmacy board may have oversight of all drug dispensing regardless of profession. Therefore, in some states, the pharmacy board has oversight of medication-related professional activities that veterinarians are engaged in which would include compounding.

The amount of oversight and available data from each state varies greatly. One example of a state program is the Missouri BOP. In 2003, the Missouri BOP started a program that tests a sample of compounded products each year of several different drug types and dosage forms. In 2020, the board tested 57 compounds for potency and, if applicable, sterility and endotoxins. The dosage forms tested include capsules, IV solutions, inhalation solutions, injectables, oral suspensions, tablets, topical creams/ointments, and topical solutions. Of the 57 compounds tested, 11 (19.3%) compounds representing 10 different active ingredients had unsatisfactory results due to potency being outside of the allowed ±10% or USP stated range [18].

The National Association of Boards of Pharmacy provides contact information and websites for each state pharmacy board at https://nabp.pharmacy/about/boards-of-pharmacy.

State Veterinary Boards

State veterinary boards are responsible for overseeing the practice of veterinary medicine within their state. Since veterinarians are legally allowed to compound medications for their patients, veterinary boards would oversee this. However, not all states have compounding laws written into their veterinary practice act, which can make this a gray area.

The American Association of Veterinary State Boards provides contact information and websites for each state veterinary board at https://www.aavsb.org/public-resources/find-regulatory-board-information.

Compliance Policy Guides and Guidance for Industry Documents

Other important concepts to define are CPGs and GFIs. The FDA issues CPGs and GFIs when it determines something is illegal but necessary under certain circumstances or they determine that a topic requires additional clarification. These documents indicate the FDA's current regulatory priorities and are subject to modification and withdrawal. They do not have the force of law. However, they are often the best indicator available of how the FDA intends to enforce various regulations and may be used by states to guide their compounding regulations. While CPGs and GFIs appear similar, they are written for different audiences. CPGs are written to guide inspectors on what to look for during inspections, while GFIs are written to guide the industry on compliance.

For practical purposes, both types of documents provide insight into the FDA's current thought process and should be used to guide compliance with the regulations.

CPGs and GFIs are used when the FDA plans to exercise its regulatory discretion. The following is a daily life example of this concept.

> In a specific area, the speed limit is 50 miles per hour (mph). However, the local police department has decided that they will only pull someone over for speeding if they are going faster than 60 mph. Since the speed limit is 50 mph, it is illegal to go faster than that. However, the police department is exercising its regulatory discretion by choosing not to enforce the speed limit unless someone is exceeding it by more than 10 mph.

What Is Compounding?

The exact definition of compounding varies depending on whether the FDA or the USP definition is being referenced. The FDA defines compounding as, "the process of combining, mixing or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding includes the combining of two or more drugs. Compounded drugs are not FDA approved" [19]. In Section 503a of the FD&C Act, which applies to patient-specific compounding, the FDA states, "as used in this section, the term 'compounding' does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling" [19].

Historically, the USP defined compounding as, "The preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice" [20]. However, with the 2022 revisions, the nonsterile compounding definition was updated to, "combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or other altering a drug product or bulk drug substance to create a nonsterile preparation." The updated Chapter <795> goes on to state that the following are not considered compounding:

- Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling
- Repackaging of conventionally manufactured drug products
- Breaking or cutting a tablet into smaller portions
- Preparation of a single dose for a single patient when administration will begin within 4 h [21]

These updates bring the USP and FDA definitions in line with regard to what is and is not considered compounding. Table 1.1 shows the difference in compounding definitions between the two USP versions and the FDA version. It should be noted that other groups such as AVMA have provided definitions of compounding, and these may vary from the USP and FDA definitions.

In contrast, manufacturing is defined as, "The production, preparation, propagation, conversion or processing of a drug or device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis and includes any packaging or repackaging the substance(s) or the labeling or re-labeling of its

Table 1.1 Examples of compounding based on the FDA and USP definitions.

Example	Compounding under the FDA definition	Compounding under the old USP definition	Compounding under the new (2022) USP definition	Notes
Reconstituting Clavamox (amoxicillin/clavulanate) powder for suspension with 14 ml of water to a final concentration of 62.5 mg/ml with a 10-d beyond-use date when stored in the fridge **which is in accordance with the manufacturer's labeling**.	No	Yes	No	This is an example of preparing a medication based on the manufacturer's labeling.
Reconstituting doxycycline powder with **25 ml** of water to make a **10-mg/ml** suspension that can be stored at room temperature for 2 wk when the manufacturer labeling indicates using **50 ml** of water for a **5-mg/ml** suspension.	Yes	Yes	Yes	This is another example of reconstituting an antibiotic, but there are changes from what the manufacturer's labeling indicates. By adjusting the final concentration of the product, it now falls under compounding based on the FDA definition in addition to the USP definition.
Crushing 250-mg metronidazole tablets and mixing with water to make a 50-mg/ml oral suspension.	Yes	Yes	Yes	This is manipulating a commercial product in a way different than the approved labeling.
Drawing up a ketamine bolus dose to be given immediately.	No	No	No	This is preparing a drug for immediate administration.

container and the promotion and marketing of such drugs or devices. Manufacturing also includes any preparation of a drug or device that is sold for resale by pharmacies, practitioners, or other persons [22]."

The main difference between the compounding and manufacturing definitions is that compounding is designed to be patient-specific and based on a practitioner's order or prescription, and manufacturing is not. Therefore, traditional compounding should not look like manufacturing. However, there are instances where compounds are needed on a large scale and/or on hand in a practice for immediate use. In these cases, the amount of dosage units being prescribed and the fact that they may be kept on hand in a practice causes their preparation to look a lot like manufacturing. That is where the Drug Quality and Security Act (DQSA) comes into play by defining the requirements for preparing large quantities of compounded products. A future section will discuss how this act affects compounded medications for veterinary patients.

The Food, Drug, and Cosmetic Act

The FD&C Act that was originally passed in 1938 became the first piece of legislation to require that drugs be proven safe. In 1968, the act was amended to include veterinary medications with the intention of requiring them to be safe, effective, and not leave residues in the human food supply. At that point, it became unsafe and, therefore, illegal to utilize medications in any way other than what the FDA-approved labeling indicated. Therefore, medications had to be used within the following constraints:

- An FDA-approved drug labeled for use in animals
- Used in the species (and any additional qualifiers such as age, reproductive status, etc.) for which it is labeled
- For the labeled indication
- At the dose and frequency indicated on the label
- For the labeled duration

These restrictions were impossible to comply with in veterinary medicine. However, the FDA acknowledged that there were instances when extra-label use is necessary in veterinary medicine. Therefore, they issued two CPGs: "Extra-Label Use of New Animal Drugs in Food-Producing Animals" that addressed food animals and "Human-Labeled Drugs Distributed and Used in Animal Medicine" that addressed nonfood animals. Eventually, these were given the force of law as the Animal Medicinal Drug Use Clarification Act (AMDUCA).

Animal Medicinal Drug Use Clarification Act

The AMDUCA is a pivotal piece of legislation from 1994 which legalized extra-label drug use (ELDU) with certain restrictions. The AMDUCA divided patients into food animals and nonfood animals based on intended use and described when off-label use would be appropriate for each group.

The following outlines when ELDU is legal in each group. It is important to note that it is required for a valid veterinarian, client, patient relationship to be in place prior to any ELDU.

Nonfood animals

1) The first product choice should be a veterinary-approved product used as labeled or extra-label use of a human-approved drug according to the labeled veterinary dose.
2) When a product cannot be used as labeled, a veterinary-approved product or human-approved product can be used in an extra-label manner.
3) If there is no approved product that can be used as labeled or extra-label, then a compounded product can be used. When utilizing a compounded medication, it is important that there is a clinical justification. Compounding a mimic product is only acceptable when the approved product is not available. Compounding a mimic for economic reasons is not legal [23]. Valid reasons for compounding include the following:
   a) Dose: When the commercial product cannot be used to administer the appropriate dose. For example, piroxicam is available as a human product in 10- and 20-mg capsules. However, at a dose of 0.3 mg/kg in dogs, many patients require a smaller dosage than 10 mg.
   b) Dosage form: Patients may require a liquid medication when the only approved products are tablets.

c) Compliance issues: When patients are difficult to medicate, this can lead to decreased compliance which decreases drug efficacy and can lead to resistance in the case of antibiotics or disease exacerbation. Compounds can be utilized to provide a flavor and/or dosage form that is more readily accepted by the patient such as a flavored liquid or a chewable treat.
d) Avoidance of allergens/toxic ingredients: When patients are allergic to an inactive ingredient or the commercial product contains a toxic inactive ingredient, compounds can be utilized to provide a version of the medication that the patient can tolerate.

Food animals: In addition to the guidelines below, there are certain drugs and drug classes that are banned from extra-label use in food animals.

1) The first choice should be to use a veterinary-approved product according to the label. This includes observing the stated withholding and/or slaughter withdrawal times.
2) If a product cannot be used as labeled, the extra-label use of a veterinary-approved product labeled for use in food animals is the next option. By using a product labeled for food animals, it provides a starting point for determining an appropriate withdrawal/withholding time.
3) If a food animal product cannot be used, the extra-label use of a veterinary-approved, nonfood animal drug or a human-approved medication can be considered. This is only acceptable if a withdrawal/withholding time can be determined in collaboration with FARAD.
4) The last resort is use of a compounded product made from an approved veterinary or human drug.

Since compounding for food animals should only be done as a last resort, the remainder of this text will focus on nonfood animals.

Preparing Compounds from an Approved Product or a Pure Drug Powder

From a compounding perspective, AMDUCA and ELDU are important because compounded medications are not FDA approved, which means they were not legal prior to AMDUCA either. The AMDUCA mentions compounded medications 11 times, but only defines them as being created by modifying an FDA-approved product. This means that AMDUCA legalized creating a suspension by crushing commercially available tablets but did not legalize preparing the same suspension from pure drug powder. Pure drug powder may also be referred to as bulk chemical or active pharmaceutical ingredient.

While some compounded medications can be prepared by manipulating a commercially available product, there are several instances where this may not be feasible or appropriate. A few examples of this are as follows:

– The commercially available product is on backorder: If the reason for compounding is because the commercial product cannot be obtained, the commercial product cannot be used to prepare the compound necessitating the use of bulk chemical.
– There is no approved product with that active ingredient: Historically, this was the case for potassium bromide, which was widely used, but not FDA approved until 2021. Another example is cisapride, which was FDA approved as a human medication at one point but was then pulled from the market in 2000 [24].
– The approved product is not feasible to use: This is the case when the only approved product is a chewable tablet, which will not make a high-quality compound due to the inactive ingredients. This can also occur with some coated tablets. Another example would be: if a liquid commercial

product is too dilute for practical administration, it is not practical to use as the drug source for making a more concentrated product.
– The patient has an allergy or intolerance to an inactive ingredient in the approved product: In this case, the purpose of compounding is often to avoid the ingredient the patient is allergic to or cannot tolerate. Therefore, the commercial product cannot be used.

While the above examples illustrate why it is not always possible to create a compound by manipulating the FDA-approved product, that does not change the fact that the AMDUCA did not legalize it. Since the AMDUCA was passed, there have been several versions of CPGs and GFIs that attempted to address compounding from bulk chemicals. However, at the time of writing, there is no clear regulation, and the topic remains controversial and changes frequently. The reader is advised to consult current state and federal regulations to determine legality of using bulk chemicals to compound.

Federal Versus State Law [8]

Patient-specific compounding is under the jurisdiction of the states like most other licensed health care activities. In contrast, human office use compounding is under the jurisdiction of the FDA. However, this was not always clearly defined as multiple judicial cases in the early 2000s led to confusion about which compounding practices were under federal versus state oversight. At the time of writing, where veterinary office use compounding falls is unclear. This means that federal compounding regulations are limited and often big picture, and exact details of compounding are left to each state to determine. Practically, most of these state compounding regulations are enforced by each state's BOP since the majority of compounding is performed by pharmacists. However, state veterinary boards may choose to include compounding topics in their practice act as well, which would apply to veterinarians preparing compounded medications in their practices.

It is important to be aware of what your state's compounding regulations are and determine how to comply. It is recommended to consult both the veterinary practice act and the pharmacy practice act in your state. When federal and state laws differ, the stricter law must be followed. It also varies by state whether the pharmacy board has any oversight of veterinarians preparing compounded medications. Therefore, it is advisable to determine which regulatory agencies oversee drugs in veterinary practice in your state. Regardless, it is good practice to be aware of and comply with state pharmacy compounding regulations. These regulations are designed to ensure high-quality compounds for both humans and animals making them applicable to veterinarians as well even if not enforceable.

One caveat to consider when looking at state regulations is how they incorporate USP standards. Some states do not incorporate USP at all and instead write their own compounding standards into their practice acts. These standards are similar to, but often not identical to the USP standards. However, other states reference USP by stating that they require compliance with USP chapters 795 and 797. For states that have their regulations written this way, the compounding requirements are subject to change whenever USP publishes chapter revisions. While major revisions are infrequent and involve significant stakeholder input, it is important to be aware of the changes if you are in a state that incorporates USP into state regulations by reference.

Another area of state oversight to consider is that states require pharmacies shipping medications into the state to be licensed with that state. Therefore, if a prescription is placed with a pharmacy in Pennsylvania and they will be shipping it to a clinic or patient in Maryland, the pharmacy

also needs to be licensed in Maryland. For some states, licensure requires that the out-of-state pharmacy follow the same regulations as in-state pharmacies, but how this is enforced varies widely. Other states only require the pharmacy to meet the requirements in the state in which they are physically located, and a few states require the pharmacy to comply with the compounding regulations in both the state where they are located as well as the state granting the license. Still additional states may compare their state regulations to the regulations of the state where the pharmacy is located and determine if they are comparable and then determine compliance requirements. To further complicate matters, what each state does is subject to change. For enforcement, most states have some type of inspection requirement for out-of-state pharmacies that are shipping sterile compounds into the state, and these requirements may or may not align with the in-state pharmacy inspection requirements. The requirements range from no specified frequency to required yearly inspections. Nonsterile compounding pharmacies may or may not be subjected to the same inspection requirements as sterile compounding pharmacies. Best practice is that out-of-state pharmacies are inspected at the same frequency as in-state pharmacies, but this is not necessarily the case. While a few states will inspect out-of-state pharmacies or identify acceptable third parties to complete the required inspections, many states rely on the regulatory agency where the pharmacy is located to conduct the inspections as they may not have the legal authority to conduct inspections of pharmacies located out of state.

Office Use Compounding

Compounding is intended to be the preparation of a unique medication to meet the needs of an individual patient. Therefore, it stands to reason that compounded medications should have the individual patient identified by way of a prescription prior to preparing the compound. In fact, that concept is included in both the FDA and USP definitions of compounding. However, sometimes compounded medications are needed urgently. Therapy cannot be delayed while waiting for the compounded medication to be prepared, especially if the medication is being prepared by another location and will require shipping. In those cases, it is necessary to have a compounded medication prepared and on hand for use in the office in anticipation of a patient needing it. This is the reasoning for office use compounding. Office use compounding is the process of having medication on hand that was not compounded for a specific patient to meet these needs [25]. Examples where office use compounds may be necessary include the following:

- Metronidazole 50-mg capsules for starting immediate treatment in a patient that is too small to dose with the 250-mg human tablets
- Diluted ephedrine for emergency administration to small animal patients
- Diluted acepromazine for use in small patients
- Enrofloxacin suspension for a patient that is not able to be dosed with the tablet or injectable formulations
- CaEDTA for use in raptors with lead poisoning

While there is clearly a need for office use compounds, there are additional risks when utilizing compounds that are not prepared for a specific patient. Traditional compounded medications are not required to be tested to prove that they are stable and contain what they are labeled to contain. When compounding, many ingredients look similar, making it possible to accidentally select the wrong ingredient. While there are checks in place to avoid this error, human error is still possible. When compounding for an individual patient, if an error occurs, it only reaches that one patient.

However, if an error occurs when preparing a batch for office use, that medication may be distributed to several patients, making the impact of an error more significant. Therefore, office use compounding needs must be weighed against the potential risk for a risk–benefit analysis. For this reason, regulations at both the state and federal levels address office use compounding. At the federal level, there is the DQSA. State regulations regarding office use interpret and/or further define acceptable office use in conjunction with the DQSA.

Drug Quality and Security Act [26]

Office use compounding was historically regulated by the states. However, after the meningitis outbreak in 2012–2013, the FDA decided that there needed to be federal oversight for large volume compounding facilities that are distributing sterile products throughout the country. The result is the DQSA, which splits compounding pharmacies into two groups. These are 503a or traditional compounding pharmacies and 503b or outsourcing facilities. Pharmacies licensed as 503a pharmacies compound in the traditional sense where they make patient-specific medications pursuant to a prescription. In contrast, those licensed as 503b outsourcing facilities are manufacturing compounded medications. These outsourcing facilities were the FDA's answer to regulating sterile compounds being distributed throughout the country for office use. As such, outsourcing facilities are overseen by the FDA, in addition to the state boards, and they need to prepare sterile compounds. Because these facilities must comply with manufacturing standards, small, patient-specific batches are not practical. To meet the needs of unique patients, traditional compounding pharmacies prepare small batches of unique medications.

At the federal level, the DQSA indicates that office use compounds must be prepared by a 503b outsourcing facility. However, the DQSA does not apply to preparing compounds for veterinary patients, and there is not any similar law that does apply to veterinary patients. This puts the legality of office use compounding for veterinary patients back at the state level. However, there are still multiple gray areas surrounding office use in several states:

- Some states indicate that office use compounding is not allowed by 503a pharmacies and do not differentiate between veterinary and human office use compounding.
- Some states have office use regulations that align with the DQSA for human compounding and have different regulations for veterinary compounding. This can lead to confusion at the individual compounding pharmacy level when they prepare compounds for both humans and animals. These regulations vary based on how states evaluate the risk–benefit ratio. For example, some may determine that benefit outweighs risk when administering the medication in hospital and dispensing enough to treat the patient while waiting for a compounding pharmacy to prepare and ship the medication based on a patient-specific prescription. After that initial time frame, the risk may outweigh the benefit since a patient-specific prescription could have been obtained.

Finding Additional Information

Due to the ever-changing nature of compounding regulations, and the wide state-to-state variability, this chapter does not go into detail about exactly what the regulations require. However, the following references shown in Table 1.2 are where you can find more information on current regulations.

Table 1.2 References for information on current compounding regulations.

Reference	Link	Information available
USP Website	http://www.usp.org	– Background information on USP – Current expert committee members – Updates on chapter updates in progress and key dates for comment submission – USP publications available for purchase
USP Compounding Compendia	Purchase at https://www.usp.org/products/usp-compounding-compendium	– Compounding chapters – Compounded Preparation Monographs
State Pharmacy Boards	List of all websites found at: https://nabp.pharmacy/about/boards-of-pharmacy	– State regulations
State Veterinary Boards	List of all websites found at: https://www.aavsb.org/public-resources/find-regulatory-board-information	– State regulations
AVMA	http://www.avma.org	– News and position statements on compounding legislation – Summary of state office use laws – AMDUCA ELDU requirements
FDA	http://www.fda.gov	– GFIs and CPGs – Warning letters issued to compounding pharmacies – Current and resolved drug shortages – New drug approvals – Approved animal drugs and marketing status – Approved human drugs and marketing status – Appropriate drug disposal – Indexed drugs for Minor Use/Minor Species – Adverse event reporting – Compounding risk alerts
DailyMed	https://dailymed.nlm.nih.gov/dailymed	– Package inserts for FDA-approved human and veterinary medications. **Note:** package inserts differ depending on the manufacturer.
AMDUCA	https://www.ecfr.gov/cgi-bin/text-idx?SID=054808d261de27898e02fb175b7c9ff9&node=21:6.0.1.1.16&rgn=div5	– ELDU requirements

Table 1.2 (Continued)

Reference	Link	Information available
DQSA	https://www.fda.gov/drugs/human-drug-compounding/text-compounding-quality-act	– 503a pharmacies versus 503b outsourcing facilities
cGMP	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211	– Requirements for medications prepared by 503b outsourcing facilities and for manufacturing approved medications

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