Compounding is Confounding!
Dawn M Boothe, DVM, MS, PhD, Dip ACVIM (Internal Medicine), ACVCP (Clinical Pharmacology)
College of Veterinary Medicine, Auburn University
Auburn, AL

Introduction
Individualized drug therapy increasingly is being recognized as an important aspect of health care for both human and veterinary medicine. Compounding has been defined by the National Association of Boards of Pharmacy (Model State Pharmacy Act) as the preparation, mixing, assembling, packaging, or labeling of a drug or device, as the result of a practitioner’s prescription drug order (or initiative) and based on the practitioner/patient/pharmacist relationship [http://www.iacprx.org/index.html, accessed July 2004]. Among the controversies surrounding compounded products is the use of bulk substances. A bulk drug substance is legally defined [21 CFR 207.3(a)(4)] for both human and animals as “any substance that is represented for use in a drug and that, when used in the manufacturing, processing or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug.” In laymen’s terms, any drug or drug preparation ingredient not prepared in an approved finished dosage form is considered to be a bulk substance. Compounding pharmacists stress that the quality of some products is markedly improved when using a bulk substance. The FDA perceives that compounding from bulk substances increases the risk of adversity. A major reason is the lack of quality assurance of compounded products. Among the reasons potentially contributing to poor quality is the bulk substance, the majority of which come from Asia and for which, for some products, contamination has been identified. The availability of bulk substances also facilitates the manufacturing (rather than compounding) of compounded products that several nationally recognized pharmacies implement. A search of internet pharmacies demonstrates that many products continue to be compounded that mimic commercially available approved products.

Compounding is as old as drug use. A major event in the profession of pharmacy and the science of compounding was the development of drug standards. In the 19th century, the United States Pharmacopeia (USP) began its role in the provision of drug standards, thus assuring strength and purity of drug materials. It maintains this often unrecognized, yet critically important role today; its pharmacopeia (United States Pharmacopeia/National Formulary; USP/NF) contains the legal standards recognized by the Food and Drug Administration. Compounded products predominated into the twentieth century; as late as the 1930s and ’40s, 50 to 60% of human drugs were compounded by pharmacists. However, in the late 19th century, the need for new, therapeutically useful compounds led to the advent of pharmaceutical research, and shortly thereafter, pharmaceutical manufacturing. By the 1950s, advances in manufacturing technology led to the mass production of drugs, causing pharmacists to largely become dispensers, rather than compounders, of drugs. The 1980s and ’90s were accompanied by a resurgence in compounding in human medicine for a variety of reasons. The history of veterinary compounding has paralleled human compounding. The cost of approval of an animal drug surpasses $15-20 million. The economic return of animal drug approval not surprisingly is low (generally well below $100 million); subsequently, the financial incentive to pursue animal drug approval compared to human pharmaceuticals is much less. Further, because of cost differences, veterinarians often will prescribe human generic drugs. Despite the fact that it should not be, compounded preparations are often prescribed because they can be cheaper. The issues with veterinary compounding include are not necessarily encountered in human compounding. Unfortunately, animal caregivers, veterinarians and pharmacists often are unaware of these differences.

Definition and Regulations for Compounding

While the FDA does not regulate the act of compounding, it does regulate the product. The advent of pharmaceutical manufacturing in the early 1900s increased human exposure to drugs, and thus the risk of adverse drug events. In the late 1930’s, over 100 persons died after being treated with sulfanilamide prepared...
in a toxic vehicle. The resultant public outcry was instrumental in the passage of the 1938 Food, Drugs and Cosmetic Act (FDCA), which addressed drug safety. In 1962, the FDCA was amended to include the assurance of drug efficacy in the mandated activities of the FDA. As in 1938, neither compounding nor animal drugs were specifically addressed. It was not until 1968, with amendment of the FDCA by the Animal Drug Amendment, that animal drugs were distinguished from human drugs. This amendment provided for the formation of the Bureau (later renamed to Center) of Veterinary Medicine (CVM) within the FDA. The mission of the CVM, as mandated by Congress, was (is) assurance of both animal and public health resulting from drug use in animals. Regulatory actions of the FDA are delineated in congressionally approved acts or their amendments. The regulations (“rules”) established for implementation of the FDCA and its subsequent amendments are published in codified form in the Code of Federal Regulations (CFR), which is available for public review. To facilitate understanding of the regulations by FDA staff, and to a lesser degree, industry and the public, the FDA may publish Compliance Policy Guides (CPG) for each set of regulations. The CPGs direct FDA regulatory actions but are not legally binding, and are open to interpretation by the FDA.

**Compounding of Human Drugs**

Compounding of human drugs was not specifically addressed in either the original FDCA or its 1962 amendment. However, the FDA is empowered to regulate any drug (or any product intended to be used as a drug) and interprets a compounded drug to be an unapproved, new drug. As compounding increased toward the end of the 20th century, FDA regulation of the human drug compounding was specifically addressed in 1997 with passage of the Food and Drug Administration Modernization Act (FDAMA). This Act, which does not apply to veterinary medicine (compounding of animal drugs is addressed below), included Section (503A) entitled “Pharmacy Compounding”. However, in order to protect consumers, the Act also attempted to provide the FDA with criteria by which inappropriate compounding could be identified and subsequently regulated. The intent of FDAMA was “to ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding.” These included the amount of drug product compounded in anticipation of need, whether or not the compounding of the drug was individual-patient driven, and, because it was perceived by the FDA as an indication of manufacturing of inappropriate amounts of a compounded product, it prohibited their advertisement. However, this aspect of the law was subsequently challenged by the pharmacy profession, based on infringement of the second amendment (right of free speech). Ultimately, the US Supreme Court agreed and because the advertisement portions of the laws could not be easily separated from the remainder of the law, the entire Pharmacy Compounding section of FDAMA was invalidated. The CPG for FDAMA stated that compounding of human drugs from bulk substances will be tolerated as long as an approved finished version of the drug exists. Ironically, with the invalidation of the Pharmacy Compounding section of FDAMA, while gaining the right to advertise their expertise, pharmacists have subsequently failed to gain protection of their right to compound human drugs (Gibbs 2002), including compounding from bulk substances. Despite the lack of legal protection, the CPG for FDAMA as currently written do indicate tolerance of the FDA toward compounding from bulk substances if an approved version (human) of the bulk substance exists.

**Compounding of Veterinary Drugs**

Pharmacists may not be aware of regulatory differences between animal and human drugs (and may not realize that CPGs are not legally binding). As such, they often assume that compounding of animal drugs from bulk substances is legal as long as an approved animal version of the drug of interest exits. In contrast to compounding of human drugs, federal regulation of veterinary compounded veterinary drugs is specifically and legally allowed by the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 (21 C.F.R Section 530; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfsearch.cfm?fr=530.41). As the animal counterpart to FDAMA, it amends the FDCA. The major benefit of this act to the veterinary profession was legalization of the
already common practice of extra-label drug use (ELDU) in animals [(Sec 512 (a) (4))], as long as the conditions stipulated in the regulations are met. AMDUCA stipulates that compounding must be performed by either a licensed veterinarian or pharmacist (thus assuring the rights of both professions to compound) in the context of a valid veterinary-client-patient relationship and that no approved dosing form or concentration of the drug (human or animal) commercially exists for the treatment of the diagnosed condition. (https://www.avma.org/KB/Resources/Reference/Pages/AMDUCA.aspx).

The interpretation and implementation of compounding regulations of AMDUCA are delineated in CPG 608.400: Compounding of Drugs for Use in Animals. The 2003 CPG describes those activities not considered to be compounding. These include mixing, reconstituting or other acts [on the drug] that are performed in accordance with the approved labeling provided by the manufacturer. Thus, any modification in the finished dosing form of the approved drug that is not specifically delineated on the drug label (which includes its accompanying package inserts) is considered by the FDA as compounding. The FDA considers any compounded product (human or animal) to be a new, finished (that is, ready for administration) drug, and, because it undergoes no federally-mandated approval process, an unapproved drug. The FDA assumes that both public and animal health potentially are at risk if compounded drugs are administered to veterinary patients since the drugs are not accompanied by “adequate and well controlled safety and effectiveness data,” particularly if not compounded in “adherence with pharmaceutical chemistry and current good manufacturing practices” (CPG Section 608.400). The FDA anticipates that compounded products may cause adverse reactions or contain potentially harmful excipients, and that the unscientific assignment of withdrawal times to compounded food animal products may lead to potentially harmful tissue residues. Accordingly, the laws (e.g., AMDUCA), regulations and CPG that address compounding of animal drugs focus (although not exclusively) on protection of human (public health) safety.

Several sources of active ingredients are used for compounded animal drugs. Legal sources are limited to FDA-approved finished forms of either animal or human drugs; the FDA makes no distinction as to which (animal versus human) is the preferred source. Because no other source is legalized, all other sources are considered by the FDA to be illegal, including non-FDA approved finished drug products obtained outside of the United States and bulk substances. Whereas AMDUCA regulations specifically state that ELDU of drugs compounded from an approved animal or human drug is permitted, (21 C.F.R Section 530), it further states that “nothing (in [Part 530]) shall be construed as permitting compounding from bulk drugs.” This statement emphasizes that the law and its regulations do not address compounding from bulk drugs (i.e., compounding from drugs is not legalized and thus, according to the FDA, is illegal). It was included in the law, in part, because compounding from bulk substances is perceived by the FDA to place humans at an increased risk to inappropriate drug residues. It is this statement that is the focus of challenge by the pharmacy profession as it seeks Congressional action to change the FDA’s interpretation of compounding from bulk substances in animals. Confusion has surrounded the issue of compounding of animal drugs; this reflects, in a part, wording of the law. The 2003 CPG specifically state that AMDUCA does not permit veterinarians to compound unapproved, finished drug products from bulk drug substances, unless the finished drug is not a new animal drug. Because any compounded animal drug is a new (yet unapproved), animal drug, then no circumstances exist in which compounding from bulk substances is allowed (except for bulk substances delineated in Appendix A of the CPG).

In the 2003 CPG, compounding actions considered for regulatory action by the CVM include violations that may result in harm to public health (e.g., involves compounding for food animals); these are most likely to be regulated, followed by compounding that may harm animal health. Further considerations include if: 1. The health of the animal being treated with the compounded drug is not threatened and if suffering or death is not likely to result from failure to treat with the compounded product. 2. Compounding is done in anticipation of prescriptions, unless in limited amounts as indicated by a prescription issued in the confines of a veterinary client-patient-relationship. 3&4. Compounding is performed using drugs prohibited for extra-label use in either food or non-food producing animals or from drugs with a restricted distribution system (drugs whose use is restricted by the FDA, such as thalidomide). 5. Compounding occurs from drugs that are not approved (human or animal, including bulk drugs) unless the product is specifically addressed for regulatory discretion by the FDA.
in Appendix A (see below). 6. Compounding involves the use of commercial scale manufacturing equipment (implying the manufacture of large amounts of drug products, in anticipation of need, and thus not patient driven). 7. Compounding occurs for third parties with subsequent resell to individual patients. While resale of compounded products is considered illegal, some State Boards of Pharmacy allow, while others do not (see below), “for office use” products which are intended for short-term dispensing to animals (clients) when prescription availability is precluded (e.g., weekends or evenings). 8. Compounding is not in compliance with applicable state pharmacy laws. 9. Compounding results in piracy, that is, the compounded product mimics an FDA-approved (human or animal) product which is commercially available in finished dosing form and appropriate for treating the patient. Importantly, this guideline indicates that cost is not a justifiable reason for use of a compounded product that replaces a more costly, commercial product. Piracy of commercially available pharmaceutical animal products is prolific (particularly equine products but is a marked financial disincentive for pharmaceutical manufacturers to pursue approval of animal drugs. Indeed, some manufacturers that would have pursued approval of a generic animal drug product have chosen to offer compounded versions of the products instead, a decision that is illegal if not driven by individual patients. 10. The compounded label does not contain sufficient information as delineated in AMDUCA regulations and 11. In food animals: exclusion of the use of human drugs, avoidance of drug residues and scientific establishment of withdrawal times.

**Drug Quality and Security Act (DQSA)**

In 2012, an outbreak of fungal meningitis in humans was traced to contaminated injectable glucocorticoids compounded by a pharmacy. This incident, which led to 64 deaths and over 750 illness, redirected Congress towards effort to increase FDA’s ability to regulate compounding. As such, DQSA was intended to correct what the 1996 FADMA was not able to accomplish. High points of the bill, which was passed in 2013, include: exemption of compounded drugs from new drug labeling, and track and trace requirements if the drug is compounded by or under the direct supervision of a registered pharmacist and if the compounding takes place in a registered outsourcing facility (currently registered facilities can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm). Some of the differences between an outsourcing facility and a traditional compounder include the following. Traditional compounders are either pharmacists or physicians who receive orders for individuals and anticipatory compounding is limited to individuals, patients, or the physician. In contrast, outsourcing facilities are considered compounding manufacturers that can compound sterile drugs either with or without a prescription. In regard to the source of active ingredients, traditional compounders can compound from FDA approved drugs, USP monographs or a list of “positive” drugs. In contrast, outsource facilities can compound only from the FDA’s drug shortage list, or the FDA’s list of bulk compounds. The bulk compounds must be from a registered facility. Such compounding must be limited to 5% interstate sales or the state of origin must have a Memorandum of Understanding with the FDA. Neither traditional nor outsource facilities can compound from withdrawn or removed drugs, or those from the “difficult to compound” list that are considered unsafe or ineffective. To facilitate quality, traditional compounders must follow USP monographs if not compounding from the list. Outsourcers, but not traditional compounders, must follow GMP requirements and are subject to risk-based FDA inspection protocols. The facilities must report to the FDA. Other considerations of the bill include, but are not limited to the following: publication of a list of drugs (generated through an advisory committee) considered to be difficult to compound and thus might reasonably lead to an adverse effects (safety or effectiveness); improves communication between the federal government and state boards of pharmacy in regards to disciplined compounding pharmacies; removes FDAMA prohibitions; and notes that a compounded product will be considered misbranded if the advertising or promotion of a compounded drug is false or misleading. The bill also prohibits resale of a compounded drug labeled “not for resale,” or the intentional falsification of a prescription for a compounded drug.

The FDA has deemed that the DQSA does not apply to animals. The Government Accountability Office (GAO) has been given the task of addressing the relevance of the law to veterinary medicine. Currently, animal
guidelines are not likely to allow compounding from bulk unless from a specific list. In response, the AVMA has sponsored a Task Force that will advise Congress. In its most recent report, the AVMA has identified the following subjects related to compounding from bulk as “critical” for discussion/delineation: 1. Adverse event reporting; 2. Labeling/disclosure of the product being compounded to clients; 3. Office stock (to allow up to 14 days work); 4. Drug shortages/unavailability (to allow compounding from bulk and to have a notification system); 5. Compounding from bulk API; 6. Quality assurance testing; 7. Liability; 8. Drug mimics (to disallow); and 9. Compounding in the lab animal/wildlife/zoo/aquaria (removed from restriction).

State Regulatory Considerations

In addition to federal laws (AMDUCA, etc.), all actions related to pharmacy, including compounding, are regulated by State Boards of Pharmacy. However, individual states vary in the applicability of these laws to compounding veterinarians. Most, but not all states, recognize a veterinarian’s right to compound. Many states have specific regulations for veterinary compounding; in their absence, human compounding regulations apply. Rarely, State Veterinary Medical Boards regulate veterinary compounding. The regulations of the states are quite variable. Some State Boards of Pharmacies allow activities that are clearly in conflict with AMDUCA (such as allowing compounding of animal drugs from bulk substances by some states versus removal of a veterinarians right to compound by others). In light of the changes in both human and animal compounding CPG, many State Boards of Pharmacy are re-examining their rules and regulations regarding compounding. The National Association of Board of Pharmacies (NABP; www.nabp.net) is a non-regulatory organization that attempts to provide standards and conformity for individual State Boards of Pharmacy. Currently, this association is generating standard regulatory guidelines (within a model Practice Act) regarding many aspects of pharmacy practice, including compounding, which might be implemented among the states. Because the NABP has recognized the increase in veterinary drug compounding, it has begun to address problems and concerns of the veterinary profession such as compounding by pharmacists that are unaware of differences in regulatory philosophy, or “rogue” pharmacists that are indifferent to the regulations. Veterinarians that dispense or prescribe compounded drugs should become aware of the relevant state laws; (http://www.avma.org/issues/drugs/compounding/default.asp). It is noteworthy that since the passage of DQSA, several states have implemented new state laws that are intended to address some of the issues related to compounding. Among the actions are those that address compounding of office stock. According to the AVMA’s State Legislative and Regulatory Affairs Department, currently 22 states allow veterinary offices to administered compounded products, but specifically prohibit them from dispensing products compounded by a pharmacy; 5 states allow veterinary offices to administered and dispense compounded products, with selected conditions; 11 states allow administration of compounded products, but do no address office dispensing of pharmacy compounded products, and 3 states that have laws and regulations that address compounding in general but not administering or dispensing by practitioners. Seven states have no laws that address compounding.