VETERINARY COMPOUNDING – FORMULATING THE FUTURE

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Individualized drug therapy increasingly is important to the effective delivery of health care to both the human and veterinary patient. Accordingly, compounding has enjoyed a resurgence of importance to drug delivery. Contributing to the recent surge in compounding are the loss of less lucrative approved drug products as pharmaceutical companies merge, emerging special needs populations, pharmacogenomics and improvements in the standard of veterinary care. Among the legitimate benefits provided by veterinary compounding are the reformulation of drugs to facilitate dosing (e.g., flavored syrups, oral rather than injectable preparations, transdermal gels) or to reduce the risk of adverse reactions due to over dosing. This latter service has been a mainstay of veterinary compounding because of the extensive use of human drugs in animals, reflecting, in turn, the limited number of animal approved drugs.

Compounding has been variably defined by different entities, but the pertinent components of the definition include prescription driven and clinician-prescribed (or formulated). Their importance was emphasized in 1997 by the US Supreme Court’s definition of compounding as “a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient.” This definition is equally applicable to veterinary and human compounding. However, in contrast to human compounding, legal direction for veterinary compounding exists (the Animal Medicinal Drug Use Clarification Act of 1994). Neither veterinarians nor pharmacists appear to be well informed regarding the content or rationale for compounding rules promulgated by the FDA in response to AMDUCA. Indeed, the pharmacy profession has objected to the Food and Drug Administration’s perceived interpretation of AMDUCA, including the FDA’s restrictions to compounding from bulk substances, which stem from a public health perspective. The compounding profession has actively pursued legislation that will facilitate compounding veterinary products. From the author’s perspective, these tactics have included a misleading emotional appeal to the veterinary profession. “Protect the pharmacist’s right to compound” was the opening page of the IACP website in 2004. It sought veterinary support of legislation that would legalize compounding, including that from bulk substances, without FDA interference (http://www.iacpfrx.org/site/PageServer?pagename=P2C2). Yet, the pharmacists’ right to compound was not being challenged; indeed, AMDUCA guarantees that right for both pharmacists and veterinarians. Rather, what was being “challenged” was the use of bulk substances. Missing in the discussions are reasons that compounding from bulk substances might be wisely avoided. These include the CVM’s concern regarding compounding in food animals; this concern might be reduced but not necessarily avoided by a different set of rules for dogs, cats or horses (for example, how might a legal definition of a food animal assure that any animal consumed by humans in the USA would be included?). A second concern is assurance of the quality of the bulk ingredient (see ingredient source below). A third concern is the ease with which manufacturing may occur once compounding from bulk substances is approved. Indeed, FDA concern regarding the distinction between compounding and manufacturing has led the FDA to attempt to legally restrict manufacturing. The first attempt was based on restricted advertisement (promotion) of compounding services in the Food and Drug Administration
Modernization Act of 1996, which was ruled unconstitutional by a US District Court (infringement of the right to freedom of speech). Subsequent restrictions by the FDA were based on the regulatory responsibilities of the FDA, which has assumed that any compounded drug is a new, yet unapproved drug. This distinction allows legal regulatory actions by the FDA. However, in October of 2006, the Federal District Court of Texas ruled that compounded drugs were not new drugs, precluding FDA regulatory oversight. Further, compounding from bulk substances was ruled legal for non-food animals (http://www.fdanews.com/dailies/drugdaily/2_425/news/59733-1.html). The IACP has declared this a victory for consumers. In the author’s opinion, suggesting to the public that this ruling, assured that FDA approval would be expected for each compounded product is a misleading tactic if not accompanied by an explanation that compounded products undergo no pre-market assessment, even when mass produced. From the author’s perspective, the intent of the FDA is not to repress appropriate compounding but to protect the consumer from inappropriate compounding. Indeed, would a fully informed public be as willing to accept and consume compounded products?

Not surprisingly, selected compounding pharmacies have extended their compounding activities well beyond that recognized to be appropriate by the FDA, thus circumventing the approval process. Internet pharmacies sell compounded products in bulk, (http://www.wedgewoodpharmacy.com/animals/index.asp), promoting these professionally-labeled products on the internet and through the mail. Such compounding appears to not be patient driven, but in fact, manufacturing, with products prepared in anticipation of need. Warning letters from the FDA to compounding pharmacies support this concern (http://www.ppsinc.org/phcom/15warnings.htm; accessed March 2007; letter to Wedgewood Pharmacy; http://www.fda.gov/foi/warning_letters/g6167d.htm, accessed March 2007). One pharmacy that provides national compounding services to humans and veterinarians has had its DEA license revoked for “manufacturing” rather than compounding drugs (http://www.avma.org/onlnews/javma/jun06/060601i.asp; accessed March 2007). Products are formulated that copy or mimic commercially available products. Many veterinarians prescribe compounded products in order to reduce drug costs. The author has observed sale of compounded products (professionally labeled) through national veterinary distributing companies at national veterinary meetings. When queried regarding the legality of distributing compounded products, the distributor’s agent indicated the distribution was being provided as “a service” to their veterinary clients. Most recently, Congress has been asked to consider a bill (HB07-1289) that will allow unlimited production of drugs for sale to clinicians (and other in-hospital situations), including the sale of compounded products from one (“registered”) pharmacy to another. Unfortunately, evidence suggests that abuse of compounding has occurred and will rise in concern with each new loss of regulatory pathways. In preparation for this manuscript, a review of veterinary compounding websites reveals the promotion of products which mimic commercially available products. Included is the promotion of products that have no approved version in the US, and as such, illegal. Unfortunately, this abuse will ultimately do harm to the veterinary profession as it finds itself in a Catch 22: we prescribe compounded products because a commercial product does not exits; the commercial product is lacking because a pharmaceutical company has not been willing to risk approval if recovery of approval costs will not be realized, which, of course, is more likely to be the case if the compounded product is being purchased in lieu of the approved product.

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In many respects, the pharmaceutical article has come full circle. In the early 1800’s, compounded products were the only source of drug articles and lack of quality led to the founding of the United States Pharmacopeia (USP) such that standards might be promulgated to support compounding. As technology led to large scale manufacture of drugs, and the role of compounding markedly declined, the emphasis on compounding standards, but not manufacturing standards declined. However, the manufacturing revolution also led to the need for pre-market establishment of quality, safety and efficacy of manufactured drug products. Accordingly, Congress approved the establishment of the Food and Drug Administration. Today, drug compounding has enjoyed a resurgence. Yet, the need for quality, safety and efficacy of compounded products is no different than it is for manufactured drugs. Restrictions of FDA regulatory actions are not countered effectively by state Boards of Pharmacy as most of the latter focus on evidence of written protocols and paper trails for compounded products and their ingredients, respectively, rather than the compounded product itself. Some state boards of pharmacy do not regulate animal pharmacy. In response to the growing market in compounding, the USP has generated a new Pharmacist’s Pharmacopeia; two USP expert committees specifically address compounding (one for injectable products and one for non-injectable products) and a third addresses compounding specific to veterinary medicine. The USP is generating recipes for compounded products. Finally, efforts of the USP have led to the organization of accreditation boards (PCAB).

The lack of adverse event reports involving compounded drugs is often interpreted as an absence of adverse events. However, unlike manufactured drugs, adverse event reporting for compounded products is voluntary. As such, pharmacovigilance simply does not exist for compounded products (http://www.ppsinc.org/phcom/03risk.htm; accessed March 2007). Yet, more so than approved products, compounded products should lead to adverse events. Of more concern than finished dosing forms is therapeutic failure, which is more difficult to detect than adverse drug events that reflect overdosing because its detection requires: 1. a correct diagnosis (i.e., treatment was needed), 2. a monitorable clinical sign that persists with therapeutic failure; 3. monitoring of the clinical sign such that failure is detected; 4. failure is attributed to inappropriate drug delivery rather than failure to respond to therapeutic concentrations of the drug; 5. the adverse event was reported to the clinician (by owner), the pharmacist (by clinician) and the FDA (by pharmacists). The author has been offered as evidence of efficacy of novel drug delivery systems the lack of reports of failures. Is this sufficient evidence of success? Finally, contributing to the concern regarding quality of compounding products is the education of the compounding pharmacists. Compounding generally is not a core requirement of pharmacy school, but rather is taken as an elective. A recent survey indicated a loss of compounding skills within 12 months, with the majority of students tested not achieving minimal competency (Eley JG, 2007; http://www.ajpe.org/view.asp?art=aj7006132 &pdf=yes; accessed March 2007).

Limited evidence of adverse events to compounded products does exist and is likely to represent only the tip of the iceberg. Examples include the following. **Ingredient Source.** The burden of purity and accuracy for bulk substances lies with the pharmacist. When seeking assurance that all products used in a compounded meet United States Pharmacopeia (USP) or equivalent standards, some pharmacists have responded that products come from an “FDA inspected site”. Does the FDA inspect the site and thus approve all products from that site, or does it inspect the product to be used in a finished dosage form? Although substitution of generic products for pioneer products without physician approval might be standard in human medicine, the same should not be accepted in veterinary medicine if the generic is a human
generic. More disconcerting, pharmacist substitution of one active pharmaceutical ingredient for another has occurred without veterinary approval (e.g., substitution of a one opioid cough suppressant for another, substitution of one antifungal for another). Finally, are pharmacists sufficiently aware that substitution of one salt form of a drug with another salt form may not result in the same potency for the drug product? **Mathematical errors.** Mathematical errors are probably the most common reason for pharmaceutical compounding errors, and potentially the most lethal. Compounding is predisposed to mathematical mistakes because, by its nature (prescription driven, small volumes), much of the equipment and technology that facilitates accuracy and precision of finished dosing forms is not (should not be) used. The author has experience therapeutic failure in epileptic patients due to compounding of capsules which contained only 50% of the labeled anticonvulsant drug. Mathematical errors also appeared to have contributed to the recent death of horses receiving compounded clenbuterol. **Preparation and Storage Errors.** The potential sequelae of chemical reactions (oxidation, reduction, hydrolysis), changes in humidity, light, pH, presence of oxidizing trace metals, and increasing environmental temperature are well recognized by manufacturers of drugs. Yet, finding the science behind expiration dates for compounded products is difficult. What published evidence exists for stability for even the simplest of syrups? The more complicated the preparation, the more important the need for science behind the product. For example, close to 50% of potency of a fluorinated quinolone (orbifloxacin) was lost when prepared in Lixotinic®. Our lab has demonstrated lack of precision and accuracy in selected transdermal gels, particularly when stored for two weeks (e.g., morphine, lidocaine). The manufacturer of a pirated commercial omeprazole paste product has demonstrated that of 10 compounded products tested, the percentage of actual drug compared with labeled content was markedly variable; only 2 products contained within 50% of the labeled content, whereas 6 contained less than 30% of the label claim. A clinical trial of the two products in Thoroughbred race horses found the compounded product to be ineffective, whereas the commercial product was effective in controlling gastric ulcers in horses. Contributing to therapeutic failure was the inappropriate pH of the compounded omeprazole paste (pH 3.4 compared with the manufactured product at pH 8.4). Cyclosporine is a complex molecule characterized by poor oral bioavailability; oral absorption requires bile acids or special formulation as a microemulsion product. In the author’s drug monitoring laboratory, cyclosporine blood concentrations were not detectable (two different samples, two weeks apart) in one cat receiving a product compounded from an approved microemulsion human product. Following recommendations that the untampered animal approved version be used at the same dose, concentrations expected at the administered dose were detected within one week of the change in drug product. **Other evidence:** Several studies have focused on accuracy in labeling of compounded products, particularly in equine medicine. Products found to be mislabeled include omeprazole, ivermectin (both pirated drugs), ketoprofen (one product contained only 50% of the labeled content, whereas 12 of 13 contained close to 100%), amikacin (percent of labeled content ranged from 59 to 140%; none were within 10%), and boldenone (all within 15% of labeled content, but 2 of 5 contained up to 5% of impurities. **Novel Drug Delivery Systems.** As appealing as transdermal drug delivery may be, clinical sense suggests that the skin is designed to preclude drug delivery. Accordingly, prudence dictates that scientific evidence of effective drug delivery precede the use of this, or other novel drug delivery systems but few reports have been generated by the pharmacy profession (e.g.: http://www.ijpc.com/products/ProductDescription.cfm?PID=4;). Data has been promulgated by the veterinary profession for a number of drugs administered transdermally in cats. To date, only
methimazole has been demonstrated to be effective, requiring 2 to 4 weeks for efficacy. Multiple dosing may be the key, but even so, marked variability among animals leads to lack of predictable response. Fluoxetine, atenolol and diazepam have been demonstrated to be variably absorbed in cats following TD administration following multiple dosing. Accordingly, only those situations in which a clinical sign or the drug itself can be well monitored lend themselves to treatment using transdermal gels.

A Call for Partnership. The author has been told by several different pharmacists that “it is not the responsibility of the pharmacist to assure safety and efficacy of a compounded product. Rather, that is the responsibility of the prescribing clinician. The responsibility of the pharmacists lies only the preparation of that product”. Although from a literal (litigation?) sense, this approach may be true, it is not ethical. All caregivers desire to provide high quality medical care to the patient. From this clinical pharmacologist’s perspective, we should strive for the same confidence in the quality, safety and efficacy of compounded products that we do with manufactured products. Each roll player, whether it be the regulatory agencies (FDA, state boards of pharmacy), pharmacists, veterinarians and clients has the common goal of provision of the best medical care possible for the patient. Compounding clearly is vital to the veterinary profession, just as quality, safety and efficacy are vital to compounded products. As the extent of compounding increases, so does the potential risk versus benefits ratio. From the author’s perspective, approaches by which confidence might be gained are: 1. Distinguishing between manufacturing and compounding based on the number of units any one pharmacy prepares; 2. Developing an alternative regulatory oversight process for compounded products that differentially addresses each compounded product based on amount prepared; 3. Informed consent of consumers receiving or prescribing compounded products (veterinarians, clients or consumers) such that it is clear such products undergo no to limited pre-market assessment; 4. Provision of consumer education regarding the differences (risks and benefits) regarding compounding versus approved, manufactured drugs; and pharmacy educational programs which address special needs of veterinary compounding; 5. Development of a robust accreditation process that involves veterinarians, for pharmacies and pharmacists that compound drugs; 6. Development of a robust, transparent, self-regulation by compounding pharmacists that: a. assures compounding (including that in anticipation) is patient, not market, driven; b. prohibits compounding of commercially available products (including products that do not exactly mimic but are intended to replace commercially available products); c. prohibits compounding of foreign substances for which no approved version exists in the US, unless such products are imported through mechanisms that assure FDA oversight; d. assures that the quality of bulk substances (API, excipients, etc.) meets USP or better standards; e. assures adherence to state boards of pharmacy laws (whether or not the state laws address veterinary compounding); f. assures adherence to available USP standards and guidelines relevant compounded products (e.g., as has been demonstrated by Wedgewood [http://www.wedgewoodpharmacy.com/WWDueDiligence.pdf]. 7. Provision of funding support of scientifically based, unbiased, well controlled studies which support the quality of compounded products (for example general compounding recipes), expiration dates, storage conditions, maintenance of potency (e.g., using marketed flavoring systems) and studies which provide evidence of safety and efficacy of novel drug delivery systems and their report in relevant journals; 8. Naming of a collaborative group of relevant role players that examines actions necessary to assure continued delivery of safe, effective and appropriately compounded products; participation by compounding pharmacy
organizations in veterinary-affiliated groups (such as Animal Health Institute) might also be considered.

SELECTED READINGS


Brakke Consulting, Inc. Veterinary Drug Compounding in the US. July 2003. 2735 Villa Creek Suite 140; Dallas TX.


Flynn, Elizabeth A.; Pearson, Robert E.; Barker, Kenneth N. Observational study of accuracy in compounding i.v. admixtures at five hospitals American Journal of Health-System Pharmacy 1997; 54: 904-912.

IACP (International Academy of Pharmaceutical Compounding); http://www.iacprx.org/ accessed July 2007


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