Why Compounding Pharmacies Use Bulk Active Pharmaceutical Ingredients from FDA-Registered Suppliers to Make Custom Medications—and Why That's Best

FDA's new draft Guidance for Industry, Compounding Animal Drugs from Bulk Drug Substances, would virtually eliminate this scientific best practice and force compounders to make custom pet medications from finished tablets, capsules, and liquids purchased from pharmaceutical companies—if they can obtain them. This will increase costs by an average of 300%, decrease quality, increase risk, and dramatically reduce the availability of compounded medications, which are regularly prescribed and prepared by 99% of veterinarians. The result: unnecessary animal suffering and death.

Using bulk ingredients is the surest, safest, most scientific way.

When a drug is compounded to meet the identified needs of patients or groups of patients, it is the best practice to use only the ingredients necessary to produce the prescribed medication. This means starting with active pharmaceutical ingredients (API) in their purest form, and then adding only the ingredients necessary to achieve the prescribed dosage-form, strength and, if specified, flavor. Bulk ingredients are APIs in their purest, verified form, accompanied by a certificate of analysis as required by the United States Pharmacopeia and federal law. Using USP-grade bulk ingredients is the surest, safest, and most scientific way to meet the unique needs of a patient while avoiding the challenges inherent in beginning any compounding process with commercially manufactured, one-size-fits-all finished goods. The most obvious challenges of starting with finished goods include ensuring accurate potency, the presence of unnecessary inactive ingredients in the finished goods, and the significantly increased cost.

Variation in potency is unacceptably risky.

Finished pharmaceutical products are allowed a considerable amount of variance in the actual amount of active ingredient they contain; using a finished product for compounding introduces an unacceptable and possibly dangerous element of inaccuracy into the compounded medication.

To fully appreciate the issue of accuracy, it is important to understand the variances allowed in individual dosages of manufactured drugs. The relevant rules allow an average variance of ±10% to ±20% of the stated dosage on the label. This variance, however, is averaged over multiple doses (e.g. all finished capsules in a bottle) to achieve the labeled potency. But for individual dosage units—like a single pill—the allowed variance may be ±20%!

The allowable potency variance for compounds is +/-10%, however testing of most preparations compounded from bulk API typically shows potency that is within ±5% of the labeled strength. This can only be achieved by knowing the exact amount and potency of the bulk active ingredients being used as starting components. If a compounded prescription were to be made from a single dosage unit (e.g., from crushing a pill), the wide variation in the active ingredient would mean that the compounded preparation could have a variation of up to ±30%. This is far outside the range of acceptable quality assurance under the U.S. Pharmacopeia guidelines for compounding of ±10%. Having a finished compounded preparation with an active ingredient strength that is ±30% of the strength that was prescribed could result in a patient being over-medicated or under-medicated, either of which could have a significant impact on a patient's health.

Avoid unnecessary and harmful excipients.

There are other reasons that make compounding from bulk API both necessary and desirable. For example, compounding from finished tablets, capsules, or liquids would require incorporating unknown excipients into the compounded preparation. This can alter the texture, taste, and

palatability of a compounded preparation, making it more difficult to dose an animal. This also can be an issue with patients who have known or unknown allergies.

Using a finished product, such as a tablet or capsule, as a source for an API has the potential for serious health problems for patients using that medication. Because the active ingredient makes up only a small portion of the overall ingredients used in commercial tablets or capsules, it is impossible to separate the active ingredient from the other "excipients" (fillers, binders, dyes, flavorings, preservatives, and other materials). Because these excipients cannot be separated, they will be incorporated into the finished compounded medication. For example, a pharmacy can't remove red dye from a commercial tablet. In fact, many FDA-approved finished products contain excipient materials that can be toxic to different animal populations, like the sweetener Xylitol, which is toxic to dogs, or the preservative Benzyl Alcohol, which is toxic to cats. Likewise, unnecessary fillers and binders from finished pharmaceutical goods add volume to the dosage size, making it difficult to make the small dosage-sizes that are critical to administration to smaller patients like cats, rabbits, or birds.

Additional safety concerns may arise from using finished product for compounding. Microbial contamination can occur any time a drug substance is introduced to an aqueous environment. This is even more likely if there are substrates present that support microbial growth, such as bulking agents like lactose, used in the formulation of many FDA-approved finished drugs. Hazardous drug substances (HDs) make up a large proportion of compounded animal drugs and are frequently dispensed in a specific strength and dosage-form that enhances patient acceptance and reduces the risk of exposure for the person administering the drug. This provides a much safer experience for both patient and pet-owner than splitting or cutting tablets or opening capsules, where the contents may become airborne and inhaled.

Costs will skyrocket.

One compounding pharmacy, which fills hundreds of thousands of prescriptions for compounded animal medications each year, conducted an in-depth analysis of its own formulary and sales: what would happen to the cost of its compounded medications for animals if it used *only* the seven APIs FDA proposes to allow and used finished pharmaceutical goods for everything else? The result was not surprising: increased labor and materials costs would increase 50% to 3,000%. The *average* prescription cost would increase by 300%. In some cases, such as for very large and very small animals, the increase would be significantly greater. Increased cost is such a significant factor for veterinarians and pet owners that we have prepared an in-depth white paper on the subject. Imagine, for example, the added labor cost of opening a thousand capsules or finely grinding a thousand tablets to produce a less-than-ideal starting material compared with the ease and accuracy of starting with a bulk powder.

Pharmaceutical manufacturers generally won't sell their products to compounding pharmacies.

FDA knows that many pharmaceutical companies have contractual arrangements with their distributors not to sell their finished products to any pharmacies. Even though *all* compounding for animal health represents less than 6% of all drugs used by veterinarians, both pharmaceutical manufacturers and FDA claim that compounding pharmacies threaten drug development and sales of commercially-manufactured drugs, although no evidence to support that claim has been provided. FDA Guidance that dictates compounding pharmacies use about 1.5% of the APIs that represent the current standard of care in favor of purchasing finished goods from pharmaceutical companies is simply disingenuous. Compounding pharmacies are the first line of defense when manufactured medicines

are not available or are deemed by a veterinarian to be inappropriate for a patient. If proposed guidance like this were to become a reality, compounders could not step in to fill these gaps!

And where do compounding pharmacies get their bulk ingredients? They are purchased from FDA-registered and inspected facilities. These facilities are also licensed by the state in which they are located, as well as by the states they ship product into. When APIs are purchased, a compounding pharmacy receives a certificate of analysis verifying the purity and quality of the ingredients. (Pharmaceutical manufactures don't—and generally won't—provide a certificate of analysis with manufactured drugs.)

State laws, which often mirror quality standards developed by the United States Pharmacopoeia, are written to ensure potency and purity of medications used for compounding. In addition, quality accreditation organizations for compounding pharmacies like the Pharmacy Compounding Accreditation Board require proof of compliance with the highest quality-standards. In addition to meeting those standards as a "table stake" for state licensure and accreditation, specialized compounding pharmacies often go above and beyond those standards by adding more testing and inspection of APIs for identity, purity, and stability. None of this is available for FDA finished goods.

Summary

The current best practice for compounding drugs for humans and animals is to start with bulk active ingredients. FDA has not issued any guidance requiring that medication prepared for human use must begin with commercially manufactured finished goods. Yet, FDA has not explained why it thinks this is a good or better idea for animal patients. This requirement will increase costs by an average of 300%, decrease quality, increase risk, and dramatically reduce the availability of compounded medications. The result: unnecessary animal suffering and death.

For more information about the implications of FDA's Draft Guidance for Industry, read this fact sheet.