March 17, 2022

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Re: Proposed update to USP General Chapter <795> via Electronic form for submitting comments on USP's proposed General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations.

Dear Representative:

On behalf of the American Veterinary Medical Association (AVMA) and our more than 99,500 member veterinarians, we thank you for the opportunity to provide comments on the proposed revisions to United States Pharmacopeia (USP) General Chapter (GC) <795> Pharmaceutical Compounding-Nonsterile Preparations. The AVMA recognizes the USP as an industry leader in the ongoing development and review of standards on best practices for pharmaceutical formulation. The establishment of such standards leads to better consistency amongst criteria of quality, safety, and efficacy so that similar medications are available to all veterinary patients.

Veterinarians care for incredibly diverse species and populations of animals within our veterinarian-client-patient relationships (VCPR), so we need formulations for use in our patients that, can be created and administered in a wide range of settings (e.g., hospitals, mobile practices, farms, racetracks, zoos/aquaria). As such, there are provisions within USP's proposed GC <795> that are not relevant, appropriate, applicable, or practical for compounding medications for veterinary practice. We have structured our comments to first convey where we support USP's newly proposed provisions and then follow with comments pointing to areas where we have concerns.

Support for proposed revisions

Facility requirements

We appreciate that language pertaining to facility requirements has been adjusted to indicate that the person compounding must assess whether weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles should be performed in a closed system device. Compounding of nonsterile preparations that does not present such a risk is no longer required to be performed within such a device.

Hand Washing

We appreciate that, for GC <795>, USP has removed the requirement that hands and arms be washed up to the elbow because weather may make such washing unsafe for veterinarians practicing outdoors in colder climates.

Garbing

We recognize that USP indicates that gloves must always be worn and that other garbing must be appropriate for the specific compounding activity. However, it is not clear who determines what is or is not appropriate garb for various compounding activities for nonsterile preparations.

Multifunctional spaces

We appreciate that USP has adjusted language to indicate that spaces within a veterinary practice setting may accommodate activities other than compounding, as long as other activities are not occurring in the same space at the same time that compounding is occurring. This change will help many veterinary professionals, although it cannot be implemented across the entire profession, because there are practice settings in which other activities will have to occur simultaneously with compounding.

Areas of concern

Lack of veterinary-specific standard development

While AVMA fully supports quality in products compounded for non-human animals, we simultaneously advocate for avoiding unintended impacts that would compromise accessibility of compounded medications for animal patients. Currently, when all veterinary practitioners are required to comply with all existing provisions of GC <795>, the needs of veterinary patients will not be met because the diversity of veterinary practice settings within which veterinary care is delivered has not been adequately considered. The AVMA believes that provisions in GC <795> should not and—practically—cannot be applied to veterinary practitioners compounding within the scope of their professional practice, and within a VCPR, until a veterinary-specific chapter has been developed to appropriately address the compounding activities of veterinary practitioners.

Veterinary access to affordable medications with a reasonable shelf life

We understand from the pharmacy community that newly proposed beyond use dates (BUD) will severely impact the frequency with which veterinarians will need to dispose of still useful medications and purchase new inventory. Increased product turnover will increase our clients' costs for compounded medications. As cost of care increases, patient care and animal health will suffer, because clients will be forced to postpone or forego treatment of their animals. We believe this change will be most harshly felt with respect to non-aqueous medications that have had BUD of more than 180 days, but that will now be limited to 180 days.

Lack of a tiered approach to standard development that is commensurate to risk

Consideration of compounding scale

Many factors contribute to compounding risks. Standards intended for compounding for a specific patient or group of patients within a veterinary practice setting must be differentiated from those that apply to large commercial distributors, because the number of patients potentially impacted by a deviation from those standards is significantly smaller.

Compounding using FDA-approved drugs as starting material as compared with bulk drug substances

Compounding from bulk drug substances (BDS) may also pose different risks than compounding from FDA-approved, conditionally approved, or indexed products manufactured under current Good Manufacturing Practices. In veterinary practices, the vast majority of compounding is performed using FDA-approved drugs and, thereby, poses substantially lesser risk than compounding from BDS.

Implementation across practice settings

Immediate use for multiple patients

We appreciate that the preparation of a single dose is exempt from adherence to GC <795> when administration begins within 4 hours of compounding, but this exemption must also apply to multiple non-human patients. There are numerous examples across the profession where multiple patients must be administered a compounded product soon after preparation. For instance, in an aquatic setting praziquantel might be used in a bath intended to treat an entire aquarium. In an equine or livestock practice, one might mix chlorhexidine ointment with a fly repellant and apply to multiple patients within a 4-hour period. In an exotic or a zoo practice, ivermectin might be diluted with propylene glycol for use in canaries and other small birds, as well as rats, mice, hamsters, and amphibians. Similarly, ivermectin might be diluted to treat heartworms in pinnipeds and such dilutions allow treatment for a wide variety of animals. In many instances, antibiotics might be diluted to make a solution for treating large numbers of small birds, reptiles, amphibians, and small mammals. In treating toxicoses (poisoning) of livestock, much of a herd or flock may need treatment. In many of these instances, the risk of serious adverse effects, including death, exceeds therapeutic risk and may raise animal welfare concerns. In these scenarios, limiting use to a single veterinary patient is impracticable and often medically inappropriate.

Training

We agree that a protocol for training must exist for those who compound; however, some of the training requirements specified are onerous and counterproductive, including the requirement that all those who compound must read (all) USP chapters. Veterinarians in leadership roles can appropriately summarize pertinent language from USP chapters, and the relevant literature, for their staff who compound without requiring they each read all USP chapters.

Cleaning

The diversity of veterinary practice settings, including outdoor spaces, client-owned homes or facilities, and locations without typical indoor environmental controls means that USP cleaning requirements pertaining to work surfaces, walls, floors, shelving, and ceiling cannot be implemented across a significant proportion of the profession's practices, particularly when veterinarians do not own, manage, or control many of the facilities or locations in which we practice.

Water source

Similarly, given the wide variety of locations and conditions under which we practice, it will not be possible for all veterinarians to access purified water, distilled water, or water obtained via reverse osmosis to be used for rinsing equipment and utensils and, in some instances, veterinarians will not have access to both cold and hot water.

Adherence to monographs

We have been advised that USP monographs do not consistently yield the most reliable product for veterinary settings, and therefore recommend that the requirement for adherence to USP monographs be removed. Further discussion is necessary to determine when specific USP monographs should be applicable to compounding activities for non-human animal patients.

Component Selection

We note under the requirements for component selection, which describe the starting materials to be used for compounding, that all products other than API, which we assume to include conventionally manufactured products, must include a certificate of analysis. However we notice that under the requirements for component receipt, which describe what should be included with such starting materials when they are received, that conventionally manufactured products do not have to be accompanied by a certificate of analysis. We request that the requirement for a certificate of analysis be removed from both sections for starting materials that are conventionally manufactured products or that labelling of the conventionally manufactured product may be used as an alternative to a certificate of analysis as is the case for GC <797>.

Enforcement of USP Standards

We recognize that USP has consistently distinguished itself as a standard setting organization rather than an enforcement entity. However, the USP understands the regulatory impact its documents have. In California, for instance, statute AB 973 makes reference to the most current version of GC <795> and GC <797>. Consequently, any revision to USP's compounding chapters may instantaneously have significant regulatory impact on California's veterinary practitioners. Several state boards of veterinary medicine have reported that adherence to USP chapters is under their authority. In other states, state boards of pharmacy have oversight of veterinary compounding. We are aware of the need for education of both boards of veterinary medicine and veterinary practitioners beginning with the basics of compounding (e.g., what is compounding, what is the difference between compounding in a pharmacy and compounding in a veterinary clinic, what USP does and how to follow its standards). AVMA proposes that such educational efforts must first start with appropriate education aimed at introducing veterinarians to USP and compounding.

Regulatory Conflict

Those who compound for veterinary patients are consistently monitoring changes to regulation and guidance at the national, state, and local levels to remain familiar with their regulatory obligations. In many instances where conflicts in the language of such documents exist, confusion arises regarding which is the correct one to follow, particularly on topics such as BUD setting and label and documentation requirements. There are multiple instances in GC <795> where questions arise regarding USP's intentions. The AVMA requests clarification regarding the following areas of potential regulatory interaction or conflict, and AVMA encourages USP to rectify and avoid such conflicts in their standard development process.

- Does USP consider FDA CVM the appropriate regulatory jurisdiction regarding requirements for adverse event reporting for compounding for animals?
- What is USP's definition of an FDA-registered facility and where can a list of such facilities be found?
- What is USP's guidance on regarding an API obtained from an FDA-registered facility that has received a Warning Letter from FDA with substantial cGMP deviations?
- How does USP propose veterinarians resolve conflicts between USP Chapters and FDA regulations, for example 21 CFR Sec. 530.12? If the label does not provide sufficient space for both USP-required information and that required by the applicable jurisdiction, which--in USP's view--should be followed?

Divergent Funding Structures

Veterinarians are most often paid directly by clients. That payment model strongly influences what standards can be reasonably implemented within veterinary medical practices. For example, significant differences exist between retail-oriented fee-for-service private practitioners as compared with veterinarians who ensure the health and welfare of animals held under permit by non-profit societies, including rare, threatened, and endangered species. However, no sector of our profession enjoys a funding structure similar to that in human health care with widespread thirty-party payer resources available to financially support adherence to such standards. The USP's lack of a tiered approach to standard development, in favor of a one-size-fits-all approach that encompasses practitioners serving both human and non-human patients, regardless of underlying risk factors, is reasonably likely to restrict access to compounded medications for veterinary patients to clients who are financially well positioned.

Conclusion

The standards in GC <795> were developed to ensure quality in products compounded for use in humans. However, standards applied to non-human animals must be developed with deliberate consideration for the unique needs of veterinary patients and clients. Veterinarians care for incredibly diverse species and populations of animals, so we need formulations for patient use within VCPRs that can be created and administered in a wide range of settings (e.g., hospitals, mobile practices, farms, racetracks, zoos/aquaria). While AVMA fully supports quality in products compounded for non-human animals, we simultaneously advocate for avoiding unintended consequences including compliance with standards that are not feasible to implement across the profession due to the practice limitations described previously, as well as economic impacts that may compromise the health of our animal patients. When all veterinary practitioners are required to comply with all existing provisions of GC <795>, the needs of veterinary patients will not be met because the diversity of veterinary practice settings within which veterinary care is delivered have not been appropriately considered. The AVMA believes that provisions in GC <795> should not and cannot be applied to veterinary practitioners compounding within the scope of their professional practice, and within a VCPR, until a veterinary-specific chapter has been developed to appropriately address the compounding activities of veterinary practitioners. We believe the creation of a veterinary-specific compounding chapter will best bridge the gap between the USP's current approach to compounded products and the practical implementation of quality control standards by veterinary practitioners. We appreciate your consideration and look forward to continued collaboration. If you have questions or would like more information, please contact Dr. Dharati Szymanski at dszymanski@avma.org or (847) 285-6742.

Sincerely,

Janet D. Donlin, DVM, CAE
Executive Vice President and Chief Executive Officer

DS/MM/GCG