

March 17, 2022

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

Re: [Proposed Updates to USP General Chapter 797](#) via [Form for submitting your comments on USP's proposed General Chapter <797> Pharmaceutical Compounding – Sterile 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) <797> Pharmaceutical Compounding-Sterile 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., veterinary hospitals, mobile practices, farms, racetracks, zoos/aquaria). As such, there are provisions within USP's proposed GC <797> that are not relevant, appropriate, applicable, or practical for compounding medications for veterinary practice. Our comments below address specific areas of concern regarding USP's newly proposed provisions.

### **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 <797>, the needs of veterinary patients will not be met because the diversity of veterinary practice settings in which veterinary care is delivered has not been adequately considered. The AVMA believes that provisions in GC <797> 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.

In certain zoo and wildlife practice settings having greater urban-wildlife interface, the newly proposed BUD may present barriers to access and thereby pose public safety risks. Carnivore species, such as bears, mountain lions, wolves, and large ungulates such as deer, elk, moose, are involved in human-wildlife encounters. In many situations, it may not be legal, safe, or necessary to use a lethal shot from a firearm; instead, rapid and reliable chemical immobilization of the animal is required. It is critical that compounding pharmacies be able to produce drug formulations needed by veterinarians in these situations. Onerous compounding standards may make these chemical immobilization drugs cost-prohibitive, jeopardizing both human and animal life. Such compounded products are often used sporadically. Accordingly, the expiration date or shelf life of such compounded products needs to be sufficiently long to be practical. We understand that the recently proposed addition of Category 3 to allow extension of BUD through stability studies was intended to alleviate concerns regarding frequent inventory disposal. However, it is our understanding that multiple medications will now require storage at impractical temperatures to be granted such an extended BUD; in effect, this negates any benefit of conducting such studies.

#### Lack of a tiered approach to standard development that is commensurate with 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 (cGMP). In veterinary practices, the vast majority of compounding is performed using FDA-approved drugs and, thereby, poses substantially less risk than compounding from BDS.

##### *Use of preservatives*

Many FDA-approved multidose vials of animal drugs contain a preservative, which is not the case for vials of FDA-approved human drugs. The greater risk inherent with preservative-free vials should also be considered in differentiating standards that pertain to human medical, as compared to veterinary medical, practice.

##### *Heterogeneity of practice settings*

As previously mentioned, veterinarians provide care in a wide range of settings including outdoor spaces, client-owned homes or facilities, and locations without typical indoor environmental controls. The proposed standards cannot be applied to all compounding environments without drastic environmental changes that will ultimately compromise patient care and that, sometimes, are simply not possible. Development of standards that are appropriate to veterinary practice settings is necessary before they can be implemented.

### Implementation across practice settings

#### *Exemptions to compounding sterile preparations in accordance with GC <797>*

With respect to the exemptions to compounding sterile preparations in accordance with GC <797> we have several concerns. First, we believe repackaging of a sterile product or preparation from its original container into another container should be exempt from adherence to GC <797>, as is the case for GC <795>. We also oppose the requirement that mixing, reconstituting or other such acts performed in accordance with the FDA-approved label are only exempt from adherence to <797> so long as the product is prepared for a single dose. We believe that any activities that occur according to the package label should be exempt from adherence to GC <797> (as is the case for nonsterile conventionally manufactured preparations for GC <795>), regardless of the number of doses or patients treated, and that the limitation on the immediate use clause should not apply.

With respect to the requirement that any multidose compounded product adhere to at least category 2 standards, we recommend the requirements for adherence to category 2 standards be removed if administration occurs within 4 hours. We ask USP to clarify because the language in section 1.3, regarding immediate use, and 14.5, regarding multidose vials, is unclear.

#### *Facility requirements*

Mixing or diluting injectable products to have them available to treat patients expediently is very common when practicing veterinary medicine. This practice is important for efficiency, ease of use (single injection), providing multimodal sedation/anesthesia for multiple animals, and when working with a variety of species. For example, an exotic practice that treats very small species must keep dilutions of antimicrobials, NSAID's, corticosteroids, and other drugs so that patients can be accurately dosed; drawing up individual doses at very small volumes is subject to human error. Across the profession, mixtures of anesthetics are necessary to provide multimodal anesthesia. Companion animal, swine, equine, dairy, small ruminant, and exotic practices all use anesthetic mixtures, including benzodiazepenes, alpha 2 agonists, dissociative anesthetics, and opioids in various concentrations. Local anesthetics, such as lidocaine, are diluted with bicarbonate for regional anesthesia. Particularly when caring for geriatric animals, drugs and other substances may be added to a fluid bag for continued use at home by pet owners. For instance, feline practitioners commonly provide clients with fluids to which potassium chloride has been added for subcutaneous administration at home as part of the treatment of geriatric cats in renal failure.

For the reasons described previously under "Lack of a tiered approach to standard development commensurate to risk", it will not be possible for all types of veterinarians and practices to install a primary engineering control (PEC) such as a laminar workbench, integrated vertical laminar flow zone, class 2 biological safety cabinet, compounding aseptic isolator, compounding aseptic containment isolator, or a pharmaceutical isolator. It will also not be possible to implement the facility and air quality maintenance and certification requirements including airflow testing, HEPA filter testing, total airborne particle sampling and dynamic airflow smoke pattern testing required for Category 1 compounding.

In addition, it will not be possible (See Lack of a tiered approach to standard development commensurate to risk) for all veterinarians and practices to meet the category 2 requirements of a clean room suite, including monitoring requirements (e.g., total airborne, viable air and surface sampling). In

many, if not most practice settings, such adherence to Category 2 standards will not be feasible to keep products that are prepared aseptically with sterile starting materials for which no sterility testing occurs for the allotted 4 (room temp), 10 (refrigerator), or 45 (freezer) days.

### *Handwashing*

The requirement to wash hands for 30 seconds up the elbow, so that medications can be kept for longer than 4 hours, may be unsafe for veterinarians practicing outdoors in colder climates.

### *Garbing*

Use of low-lint full gowns, shoe covers, head covers, masks, and gloves in all instances of compounding; adherence to glove and fingertip sampling requirements; and aseptic manipulation competency evaluation through media fill tests will not be possible in many veterinary compounding settings (see related comments regarding settings within which veterinarians practice under “Lack of a tiered approach to standard development commensurate with risk”).

### *Cleaning*

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

### *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.

### *Glossary definitions*

Neither “preparation” nor “medication” is defined in the Glossary. The AVMA requests clarification regarding whether they refer to different articles or if they are interchangeable? Also, are they synonymous with “drug”, and if so, why are different terms used?

### 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 (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 USP standards). The AVMA proposes that such educational efforts must first start with appropriate instruction 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 regulation to follow, particularly on topics such as BUD setting and label and documentation requirements. There are multiple instances in GC <797> 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 products compounded 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 regarding use of 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 veterinarians follow?
- How does USP propose veterinarians resolve any conflicts between USDA injection guidelines and CDC guidelines?<sup>i</sup>
- How does USP propose veterinarians certify procedures in the current Controlled Environment Testing Association (CETA) Certification Guide for Sterile Compounding Facilities, or an equivalent guideline, when combining drugs from FDA-approved applications in a barn, farm, ranch, home, or other client setting that may need to be used more than 4 hours after compounding?
- USP states that conventionally manufactured sterile products should be used when available and appropriate for the intended compounded sterile preparation. How does USP propose veterinarians resolve conflicts between cGMP and the monographs?

### 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 third-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 not financially well positioned.

## Conclusion

The standards in GC <797> were developed to ensure quality compounded products for use in humans. Applying these standards to compounding for use in non-human animals is not practical. The AVMA asks for the development of guidelines that address the unique needs of veterinary patients. Veterinarians care for incredibly diverse species and populations of animals, so we need formulations for our patient's 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 would compromise the accessibility of compounded medications for our patients. When all veterinary practitioners are required to comply with all existing provisions of GC <797> the needs of our patients will not be met because the diversity of veterinary practice settings has not been adequately considered. The AVMA believes that provisions in GC <797> should not and—practically—cannot be applied to veterinary practitioners compounding within the scope of our 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 for use in humans 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 [dszymanski@avma.org](mailto:dszymanski@avma.org) or (857) 285-6742

Sincerely,



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

---

<sup>i</sup> USDA Veterinary Services. [Injection Practices on U.S. Dairy Operations, 2007 Injection Practices in U.S. Cattle Feedlots1](#). February 2009. Accessed on 2.28.2022 at [chrome-extension://efaidnbnmnibpcjpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.aphis.usda.gov%2Fanimal\\_health%2Fnahms%2Ffeedlot%2Fdownloads%2Fcofe%2FCOFE\\_is\\_Injec.pdf&clen=175811&chunk=true](chrome-extension://efaidnbnmnibpcjpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.aphis.usda.gov%2Fanimal_health%2Fnahms%2Ffeedlot%2Fdownloads%2Fcofe%2FCOFE_is_Injec.pdf&clen=175811&chunk=true)

DS/MM/GCG