Scott Brunner
President
Alliance for Pharmacy Compounding
100 Daingerfield Road, Suite 100,
Alexandria, Virginia 22314.

February 15, 2023

Dear Mr. Brunner:

Thank you for your letter on behalf of the Alliance for Pharmacy Compounding and National Community Pharmacists Association dated July 26, 2022, asking for "clarity on how the agency views the processes enumerated in the guidance document [GFI 256, "Compounding Animal Drugs from Bulk Drug Substances"]."

You raised several *specific questions* regarding GFI 256. Please see our responses below:

General

1) *Do you anticipate that the GFI will be amended to reflect clarifications that have resulted from our and others' questions and observations?*

FDA is assessing the best way to clarify certain questions raised during the outreach period. Many questions are regarding outsourcing facilities without a state pharmacy license. FDA does not intend to conduct routine inspections relating to the enforcement priorities for animal drugs described in GFI 256 at any federally registered outsourcing facility until it provides clarification regarding how the policy in GFI 256 applies to these facilities. However, routine inspections at outsourcing facilities unrelated to GFI 256 will continue.

2) *How will ORA align with CVM in its interpretation of GFI 256? Will CVM be involved in facility inspections and providing input in how auditors interpret the GFI and interact with pharmacies in the inspection process? (We believe such alignment is essential in order to assure consistent enforcement of the GFI. Without it, candidly, CVM's expressions of its view of the GFI's provisions don't amount to much. What will matter is how ORA inspects and enforces.)*

GFI 256 describes the Food and Drug Administration's (FDA) enforcement policy regarding the compounding of animal drugs from bulk drug substances. CVM and ORA are working together to ensure that inspectors understand the guidance and to provide inspectors with detailed instructions on how to conduct animal drug inspections consistent with the guidance.

3) *From a policy implementation perspective, are OCQC and CDER in harmony with CVM on interpretation and enforcement of the GFI, or is the GFI to be a distinct effort by CVM? (Same comment on this question as on the previous one. Alignment is essential.)*

GFI 256 describes the Food and Drug Administration's (FDA) enforcement policy regarding the compounding of animal drugs from bulk drug substances. FD&C Act provisions that apply to compounding of human drugs do not apply to compounding of animal drugs. CVM and OCQC work collaboratively to minimize confusion and disruption from the implementation of different federal statutory requirements at pharmacies that compound both human and animal drugs.

VCPR

1) *Will FDA expect compounding pharmacies to ensure there exists a "valid" VCPR for each prescription received for a compounded medication? If yes, please confirm that a representation by the prescriber that a valid VCPR exists, consistent with standard practice, would be sufficient evidence?*

Compounding pharmacies may continue to rely on veterinary prescriptions under their state requirements. FDA does not generally expect compounding pharmacies to confirm a valid VCPR exists. FDA may expect additional verification if the pharmacy has reason to believe there is not a valid VCPR.

2) *Is the lack of availability of a human or animal drug that is FDA-approved, conditionally approved, or an indexed drug a valid reason for a veterinarian to determine that a medical need exists for a compounded medication? While footnote 9 of the GFI mentions FDA's intentions related to mitigating temporary drug shortages, it does not clarify FDA's enforcement position for pharmacies or veterinarians in situations where FDA-approved, conditionally approved, or indexed drugs are not actually available in the supply chain due to manufacturer discontinuations, backorders, or shortages. While these mitigation efforts may prove effective, shortages often occur quickly and unexpectedly, and drugs are often needed quickly to treat sick animals – thus, compounding is needed to address patient needs in the short-term.*

As described in GFI 256, the unavailability of an FDA-approved product (such as when a manufacturer will not sell the product to a compounding pharmacy) is a specific reason to compound from a bulk drug substance instead of an approved product. A brief explanation regarding lack of availability should be documented as the rationale for using a bulk drug substance.

On the other hand, if there is a drug shortage (due to supply chain issues or backorders) compounding pharmacies should contact FDA by emailing AnimalDrugShortages@fda.hhs.gov.

FDA addresses each drug shortage on a case-by-case basis. GFI 256 does not provide blanket enforcement discretion to compound copies of drugs in shortage.

Policy

1) *Can FDA clarify the specific criteria or data that it will use when determining if compounded drugs present particular human or animal safety concerns? For example, are there specific APIs, dosage forms, or animal patient populations that FDA believes present higher safety concerns?*

FDA has human safety concerns with animal drugs compounded for food-producing animals due to the risk of drug residues in the meat, milk, or eggs consumed by people. Compounded animal drugs in certain dosage forms (such as transdermal) also present human safety risks for people handling or administering the animal drug.

Additionally, poor compounding practices can result in drugs that are superpotent, subpotent, contaminated with filth, or formulated with ingredients and drug formulations that present safety risks for the treated animals. FDA investigates complaints and reports of adverse events associated with use of compounded drugs and expects that compounders will investigate root causes when such complaints and reports come to them. Adverse events may also result when a product is formulated with ingredients that are harmful to the particular species, such as xylitol in dogs. Compounders are expected to know what ingredients may be harmful or cause side effects to the species for which the drug is being compounded. A drug may also present particular safety concerns if, due to specific factors related to its strength, dosage form, or formulation, it cannot be consistently compounded to meet quality standards with the equipment and practices at a pharmacy.

2) *Can FDA provide the specific standards it expects compounding pharmacies to meet as it relates to the "other manufacturing, product quality, labeling, or packaging requirements of the FD&C Act"?*

The FD&C Act contains a variety of legal requirements that apply to all drugs. For the most common standards relevant to this provision, please see FD&C Act Sections 501 and 502 and their implementing regulations.

3) *Under what circumstances will FDA deem it necessary to provide concurrent oversight of compounding practices, and specifically what level of interaction with compounding practices does FDA anticipate as being part of concurrent oversight?*

We are unable to foresee or list all the circumstances that might result in FDA needing to provide concurrent oversight or the level of interaction needed in each case. Some examples may include a state requesting FDA's assistance, an emergency that prevents a state from carrying out its normal regulatory functions, or a situation where ongoing compounding practices of concern are causing harm outside of the home state.

4) *Formulation details are generally determined by compounding pharmacists. Does FDA generally not intend to question pharmacist determinations of the appropriateness of a commercial product vs. bulk ingredient?*

FDA will review the compounder's documented reason(s) why no approved or indexed drugs can be used as the source(s) of the active ingredients. Although GFI 256 includes 3 examples of valid reasons (each of which covers a broad set of drugs/situations) compounders may identify and document other valid reasons why no approved or indexed drugs can be used. FDA generally does not intend to question the professional judgement of pharmacists.

Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

1) *Will FDA be determining a pharmacy's, pharmacist's, or veterinarian's compliance with state laws and regulations? If so, how will this be implemented?*

FDA communicates with the state entities that regulate the practice of pharmacy and veterinary medicine and generally relies on their determinations regarding a pharmacy's or veterinarian's compliance with state law. An ordinary example of how this provision would be implemented is if a state entity identifies serious non-compliance but is not able to fully remedy the violations on their own, the state may notify FDA of their determination and request assistance the observations also violation federal law.

2) *Does the term "USP-NF monograph" as used within GFI #256 include drug and dietary supplement monographs?*

The USP-NF monographs applicable to compounded drugs are the drug monographs. USP-NF dietary supplement monographs are intended only for use with respect to dietary supplements. The term "dietary supplement" does not apply to products intended for use in animals under federal law.

3) *What are the "other FD&C Act requirements" that FDA expects compounding components to meet?*

The FD&C Act contains a variety of legal requirements that apply to all drugs, including active ingredients, inactive ingredients, and finished dosage forms. For the most common standards relevant to this provision, please see FD&C Act Sections 501 and 502 and their implementing regulations.

4) *Are container-closure systems used to package finished compounded preparations included in the definition of "inactive ingredients"?"*

Container-closure systems are not included in the term "inactive ingredients." Some requirements related to containers are found in FD&C Act Section 502, and some USP-NF monographs contain specifications related to container-closure systems.

Patient-Specific Prescriptions-Dispensing

1) [Patient-Specific Prescriptions Circumstance 4] *Part (b) allows a veterinarian to dispense a compounded drug to another veterinarian within the same practice, but prohibits a pharmacy from dispensing a compounded drug to a veterinarian who did not write the prescription. Can FDA clarify if a pharmacy can dispense a compounded drug to another veterinarian in the same practice as the veterinarian who wrote the prescription? This section does not seem to acknowledge and allow for veterinarians who are mobile. Can FDA clarify that a veterinarian in the same practice but who is mobile due to the need to treat large animals, wildlife and other animals that can not come to a location may receive and dispense these drugs?*

As described in GFI 256, for patient-specific prescriptions, pharmacies should dispense a compounded drug directly to the prescribing veterinarian (which may include mobile veterinarians) or to the patient's owner or caretaker. Pharmacies should not dispense patient-specific prescriptions to a veterinarian who did not write the prescription because it is not clear that there is a valid veterinarian-client-patient relationship.

Patient-Specific Prescriptions-Copies

1) *Footnote 9 defines "marketed" as a drug that a manufacturer is making and offering for sale. For a compounded medication to be considered a copy of a "marketed" FDA-approved/indexed drug, does the FDA-approved/indexed drug simply need to be made and offered for sale by the manufacturer, or does that drug actually have to be available to the veterinarian or pharmacy? There are situations where there are supply-chain issues with FDA-approved/indexed drugs, making them inconsistently available. In these situations, compounding from finished goods is not possible and pharmacies should be permitted to compound from bulk drug substances.*

As described in GFI 256, the unavailability of an FDA-approved product is a specific reason to compound from a bulk drug substance instead of an approved product. A brief explanation regarding lack of availability should be documented as the rationale for using a bulk drug substance.

FDA addresses each drug shortage (such as supply chain issues) on a case-by-case basis. GFI 256 does not provide blanket enforcement discretion to compound copies of drugs in shortage. If compounding pharmacies have concerns about shortages of animal drugs, they should contact FDA by emailing AnimalDrugShortages@fda.hhs.gov.

2) *What resources/data is FDA using to determine if an FDA-approved/index drug is being made, offered for sale, and consistently available in the marketplace?*

FDA receives information from a variety of relevant authorities, including the drug registration and listing requirements (21 CFR Part 207), and distribution data reporting requirements (21 CFR 514.80(b)(4)(i), and/or 21 CFR 514.87(b)(4)-(5)). FDA is also in the process of implementing

the new CARES drug volume reporting requirement, which will provide more detailed information (please see our draft guidance "Reporting Amount of Listed Drugs and Biological Products Under Section 510(j)(3) of the FD&C Act" which, when finalized, will explain FDA's policy on drug volume reporting). In addition to our legal authorities, FDA communicates with sponsors, veterinarians, and other parties to gather information on drug availability. FDA also has a variety of inspectional and investigational authorities (see, e.g., FD&C Act section 704) that it can use to gather or verify relevant information from parties in the manufacturing and distribution chain.

To the extent the question relates to GFI 256, the recommendation is that compounders determine and document the reason(s) why approved drug products could not be used as the source(s) of the active ingredients (and which notes that a drug being "not available for compounding" is an acceptable reason). FDA will review the documentation provided by the compounder related to unavailability. Examples of such documentation could include emails, letters, or other correspondence with manufacturers or distributors, notes or memos documenting a compounder's attempts to purchase a drug by placing orders over the phone, etc.

3) *Can FDA confirm that prescriptions received by the pharmacy from veterinarians prior to the effective enforcement date of GFI 256 but filled or dispensed by the pharmacy after the effective enforcement date will be exempt from requiring documentation of the veterinarian's medical rationale? For example, if the enforcement date is October 1st, will prescriptions received by the pharmacy prior to October 1st but dispensed on or after October 1st be exempt from requiring documentation of medical rationale? This is important because the required systems and significant education for veterinarians to implement these determinations will not be ready prior to October 1, 2022.*

In cases where prescriptions were written prior to April 1, 2023, the earliest date on which inspections might commence, FDA does not expect compounders to retroactively obtain documentation of medical rationale before dispensing refills, provided the prescription is valid and filling it complies with all applicable laws in both the compounder's state and the patient's state (specifically, those laws governing the number of allowable refills and prescription expiration dates).

4) Can FDA confirm that the record of the veterinarian's medical rationale need only be captured once for each medication prescribed to a patient? For example, a veterinarian may issue a prescription for a medication to a patient that allows for multiple refills, or a veterinarian may issue a new prescription for the same medication and the same patient in order to continue a patient's therapy over the course of several months or years. Can FDA confirm that in these situations the record of the veterinarian's medical rationale need only be documented once on the patient's original prescription record?

The medical rationale does not need to be documented more than once if it is maintained in the pharmacy records with the prescriptions. The pharmacy should be able to verify in their records it was already obtained when accepting an identical new prescription and should be able to provide it to FDA upon request (such as a request based on recent dispensing of the new prescription).

Adverse Event and Product Defect Reporting

1) *Given the requirement to report adverse events or product defects to FDA within 15 days, it is likely that a pharmacist or veterinarian may not have completed their investigation into the issue within that 15-day window. Will FDA give pharmacists and veterinarians the ability to amend or potentially withdraw previously submitted adverse event or product defect reports? How will FDA treat a Form 1932a that is incomplete due to an investigation not being complete?*

Yes, the ability to send follow-up information is already available. Pharmacists and veterinarians may submit follow-up reports to previously submitted adverse event or product defect reports by marking the submission type on the form as "follow-up." A 15-day "initial" report is entered into our adverse event database as an "initial" report. If a follow up report is received, the initial case is amended with the follow-up information.

2) *The labeling requirements of GFI #256 require the statement "Report suspected adverse reactions to the [pharmacist or veterinarian who compounded the drug] and to the FDA using online Form FDA 1932a" to be included with individual patient prescriptions. Will FDA be following-up with pet owners who report adverse reactions directly to FDA to gather additional details or information?*

FDA may reach out to owners to collect additional information if deemed necessary; however, this is not done routinely.

3) *Will FDA be passing along any pet owner reported adverse reactions to the pharmacist or veterinarian who prepared the compounded medication?*

No. FDA CVM does not have a program to share individual adverse event reports with pharmacies or veterinarians; however, we do publish certain adverse event data on openFDA. Please note that information obtained by FDA may be subject to FOIA or Privacy Act restrictions on sharing. FDA strongly encourages complainants to share directly with compounding pharmacies, which is why GFI 256 recommends the label statement say, "Report suspected adverse reactions to the [*pharmacist or veterinarian who compounded the drug] and* FDA."

4) *Form 1932a submissions seem to only be permitted by a hard-copy form. An electronic process may make the data much more usable and make submission more streamlined. Will FDA amend this process to make it consistent with modern day reporting?*

Form FDA 1932a is available as an "electronic" form on the www.fda.gov/reportanimalae website. This dynamic fillable form can be emailed to CVM, where it can be imported directly into CVM's adverse drug event database. Improving the process further is contingent on the availability of resources and funding.

5) *Will FDA be sharing any adverse events or product defects reported by veterinarians, pharmacists, or pet owners via Form FDA 1932a with the veterinarian's or pharmacist's state licensing board?*

CVM does not have a program to share/send individual adverse events received on Form FDA 1932a with state licensing boards. Please see answer above for more details. Please note that adverse event and product defect reports may be requested through the Freedom of Information Act.

Nominations of Bulk Drug Substances for Compounding Office Stock Drugs for Nonfood-Producing Animals

1) *Prior to making a decision on a nominated bulk drug substance, will FDA reach out to the nominator for further information/clarification?*

Yes, in certain cases. For many of the nominations requiring clarification, for example, which dosage forms are intended for use in which species, or where the need for urgent use as office stock has not been adequately demonstrated, FDA has been reaching out to nominators for additional information. FDA does not intend to reach out to the nominator prior to a decision on every nominated bulk drug substance. FDA will generally contact the nominator if there is missing information or if clarification is needed. Nominators can also provide additional information or ask questions by emailing CVMCompoundingNominations@fda.hhs.gov.

2) *Can a nominator include a range of strengths and/or dosage forms for the finished compounded medication when submitting a single bulk drug substance nomination? For example, bulk drug substance X used to prepare a 1 to 5mg capsule for the treatment of Y condition in cats; bulk drug substance A used to prepare a 15mg/ml oral liquid or oral paste for the treatment of B condition in horses.*

Yes. The nomination may include multiple dosage forms and a range of strengths and dosages. If the nomination includes more than one species, it should be made clear which dosage forms, in what strengths or concentrations, apply to each species, for which indication. Nomination submission should additionally address the other information described in the Appendix of GFI 256.

3) *If a pharmacist or veterinarian submits a bulk drug substance nomination to FDA prior to FDA's effective enforcement date of GFI #256, can that pharmacist or veterinarian continue preparing office stock compounds using that bulk drug substance until such time that FDA has reviewed the nomination and determined whether or not to approve it?*

Yes. FDA adds bulk drug substances that have been nominated (with sufficient information to review) and are under review to the **List of Nominated Bulk Drug Substances Currently Under Review.** Bulk drug substances will remain on this list only while FDA is reviewing the nomination. While these evaluations are being completed, the agency generally intends to refrain from taking enforcement action when these bulk drug substances are used to compound a finished drug in a state-licensed pharmacy or federal facility or by a state-licensed veterinarian as described in the initial nomination.

Once the evaluation for a given bulk drug substance has been fully completed, those found to meet the policy for inclusion on a list will be removed from the "Currently Under Review" status and will be added to the appropriate list for nonfood-producing animals, food-producing animals, or free-ranging wildlife species. Those bulk drug substances that are not found to meet the policy for inclusion on a list will be designated as "Bulk Drug Substances Reviewed and Not Listed."

4) *How will FDA be prioritizing its review of nominated bulk drug substances? Will nomination reviews be prioritized based on the healthcare needs of the intended species/conditions, the lack of readily available FDA approved treatment alternatives, or first come first serve?*

Nominations are received on a rolling basis and review priorities are based on treatment alternatives, animal health needs, and the availability of FDA expertise. In addition, multiple nominations of the same BDS are being combined in one review to the extent possible, regardless of when they were received, to facilitate more expeditious review. As described above in 3, FDA generally intends to refrain from taking enforcement action for BDS that are currently under review so that veterinary access to these compounded products is not restricted during the review process.

5) *In addition to providing complete information with nomination submissions, what else can nominators do to support an expedited review by FDA? For example, would submitting a small number of nominations in multiple submissions over a period of time support a quicker review process versus submitting a large number of nominations all at once?*

There is no "expedited review" process for BDS nominations. Submitting nominations in large or small batches will not affect the review time frame. Nominators should submit information that completely addresses the Appendix of GFI 25. To assure that a nomination can be reviewed efficiently:

- For *nonfood-producing animals*, nominations should include sufficient support for urgent use. By "urgent use" we mean that the drug is necessary to avoid animal suffering or death, or to protect public safety. The information provided should explain why animal suffering or death will result if treatment is delayed until a

compounded animal drug can be obtained pursuant to a prescription for an individually identified animal or group of animals.

- For *food-producing animals*, nominations will only be reviewed if the BDS is intended for use as an antidote.
- For *free-ranging wildlife*, nominations will only be reviewed if the BDS in intended for use as an anesthetic or sedative.
- Nominations of BDS for use in *minor species* (food- or nonfood-producing) with overly broad categories such as "birds," "carnivores," "assorted large and small exotic/zoo species," "free-ranging wildlife," etc., will generally not be reviewed. Each nomination should describe use of the drug in each species (or more narrowly defined species category), in each dosage form nominated, for each indication, and for nonfood-producing species, why the drug is needed urgently as office stock.

6) *FDA has said that it will quickly review submissions and place them on an "under review" list unless significant safety concerns are present. We note that there have been submissions and we do not believe FDA has acted on these submissions. Can FDA commit to a time schedule for reviewing nominations*?

We provide enforcement discretion for nominated BDS on the List of Nominated Bulk Drug Substances Currently Under Review during our review process. The initial review does not take long but the time is impacted by the completeness of information provided and the volume of nominations that we receive at the same time.

Please reach out to us at CVMCompoundingNominations@fda.hhs.gov if you have questions about a specific nomination.

Thank you for your interest in animal drug compounding, an issue of high importance for veterinary medicine. Please let us know if you have any other questions.

Sincerely,

William T. Flynn -S

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