July 26, 2022

William Flynn, D.V.M.
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Pl, HFV-1
Rockville, MD 20855

Re: Clarifying Questions Regarding GFI #256

Dear Dr. Flynn:

Thank you for your willingness to respond to our questions below about the Center for Veterinary Medicine's intentions regarding enforcement of GFI #256. We believe your answers can provide much-needed clarity on how the agency views the processes enumerated in the guidance document and can help compounding pharmacists, veterinarians, and state boards of pharmacy better understand how the agency will view compliance with the GFI.

We also believe that the questions contained in this letter demonstrate the range and depth of what is as yet unknown about the effect and enforcement of the GFI, and therefore support the recent joint letter submitted by several pharmacy trade associations requesting an enforcement delay on the GFI until at least FY2024.

We intend to communicate your responses to these questions – and the substance of the multiple conversations we have had with CVM to-date – to our members so that they can build processes and SOPs to attain compliance with GFI #256.

Due to the complexity – and some ambiguity – of the matters covered by GFI #256, however, those SOPs and policies will necessarily have to interpret and implement firm positions on questions that have not been clearly addressed by FDA. Accordingly, we expect that no enforcement action will be taken by the agency against compounding pharmacies that draft and adopt SOPs consistent with GFI #256 and the answers you've provided to these questions and others we've asked in our conversations with you and your team. To the extent that FDA disagrees with those interpretations and positions, we would also expect that compounding pharmacies will be given the opportunity to amend their practices to conform with these clarified FDA positions prior to any adverse action being taken against those pharmacies.

While we are encouraged by your willingness in the past few weeks to engage in dialogue with us and provide some clarity on our concerns about the GFI #256 framework and how it may be implemented,

we remain unsure about how our questions and suggestions may affect the GFI as released and enforcement of it. Following are questions on which APC – and the compounding profession as a whole – desires clarity. Please note that the italicized portions are excerpted directly form the GFI itself.

I. General

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

III. 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.)

IV. 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.)

II. VCPR

The policies described in this document are intended to protect human and animal health by limiting the use of animal drugs compounded from bulk drug substances when a veterinarian, acting within a valid veterinarian-client-patient relationship (VCPR), determines there is no medically appropriate human or animal drug that is FDA-approved, conditionally approved, or indexed to treat the animal (referred to as "FDA-approved or indexed drugs" in this document).

Questions:

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?
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.

III. Policy

When pharmacies and veterinarians compound animal drugs from bulk drug substances as described below, the Agency generally does not intend to take enforcement action for violations of the FD&C Act's requirements for animal drug approval; adequate directions for use; and CGMP. Nevertheless, FDA intends to prioritize enforcement of these provisions when: (1) the animal drugs are compounded outside the circumstances described below; (2) the compounded drugs present particular human or animal safety concerns; or (3) the compounded drugs do not meet other manufacturing, product quality,

labeling, or packaging requirements of the FD&C Act (e.g., if the product is made under insanitary conditions or the labeling is false or misleading). FDA will ordinarily rely on compounding pharmacies' home State licensing boards to provide day-to-day oversight of routine compounding practices (i.e., routine inspections for drug quality) but may provide concurrent oversight of compounding practices when considered appropriate by the Agency. Should FDA have cause for concern, the Agency may also refer a case to the appropriate State licensing board(s).

Questions:

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?
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"?
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?
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?

IV. Compounding for Nonfood-Producing Animals: Patient-Specific Prescriptions

The drug is compounded in full compliance with State laws and regulations governing drugs, pharmacy, and veterinary medicine

Question:

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?

All bulk drug substances, inactive ingredients, and finished drug products used in compounding meet the standards set in any applicable USP-NF monograph and comply with other FD&C Act requirements for drug components

Questions:

1. Does the term "USP-NF monograph" as used within GFI #256 include drug and dietary supplement monographs?
2. What are the "other FD&C Act requirements" that FDA expects compounding components to meet?
3. Are container-closure systems used to package finished compounded preparations included in the definition of "inactive ingredients"?

The drug is dispensed by

(a) the pharmacy, after receipt of a prescription for a specific patient from the veterinarian acting within a valid VCPR, directly to the prescribing veterinarian or to the patient's owner or caretaker or,

(b) the veterinarian to the owner or caretaker of a patient in his or her practice, or to another veterinarian in his or her practice located in the same physical location. The enforcement discretion policy described in this guidance does not apply to compounded drugs that are dispensed or transferred to a third party such as a distributor or retailer, or by a pharmacy to a veterinarian who did not write the prescription;

Question:

1. 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?

The compounded drug is not a copy of a marketed FDA-approved or indexed drug. Or, if it is a copy, there is a difference between the compounded drug and the FDA-approved or indexed drug that will produce a clinical difference in the identified patient as determined by the treating veterinarian.

Questions:

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.
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?
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.
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?

V. Adverse Event and Product Defect Reporting

Questions:

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?
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? Will FDA be passing along any pet owner reported adverse reactions to the pharmacist or veterinarian who prepared the compounded medication?
3. 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?
4. 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?

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

Questions:

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

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?
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 thank you again for your willingness to consider and share answers to these questions, and moreover, for your consideration of our request for an enforcement delay. Your responses can provide some clarity about matters on which clarity will be essential for understanding what constitutes compliance.

We look forward to your response. Please direct it to me at scott@a4pc.org or to Scott Brunner, Alliance for Pharmacy Compounding, 100 Daingerfield Road, Suite 100, Alexandria, Virginia 22314.

Sincerely,

ALLIANCE FOR PHARMACY COMPOUNDING
NATIONAL COMMUNITY PHARMACISTS ASSOCIATION