The Negatives About FDA's "Positive List."

The FDA's proposed list of bulk ingredients that may be used in compounding medications for office use with animals ("positive list") is positively certain to fail veterinarians, pet owners, and animals. It protects drug manufacturers, not animal patients. Shockingly, in its new draft Guidance for Industry #256, which includes a proposal for how to nominate additional bulk drug substances to this list, FDA creates hurdles that are ***exactly the opposite of those FDA specifies when compounding for human health****. These FDA hurdles disqualify for nomination nearly every common ingredient prescribed by veterinarians, forcing veterinarians and pharmacies to either start with FDA-approved drugs, or go through yet-to-be-determined justification and documentation of medical rationale. Clearly, this is FDA overreach into the state-regulated practices of veterinary medicine and pharmacy.*

Here is a quick picture of FDA hurdles and common medications that would be knocked out of any possibility for nomination. This graphic shows where in the six-step elimination process 36 of the 38 most frequently compounded APIs would not be eligible for nomination to the positive list:

Most common bulk drug substances **may not be nominated** for the GFI #256 positive list because they don't clear the following FDA hurdles:

	They are on FDA's Negative List. Compounding from bulk substance for these APIs is prohibited.	Amlodipine Budesonide Chloramphenicol Dexamethasone Dipyrone Doxycycline	Enrofloxacin Gabapentin Idoxuridine Itraconazole with DMSO Voriconazole
1	There is no FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;	Buprenorphine Cyclosporine Fluoxetine Methimazole Pentosan Phenylbutazone	Pimobendan Ponazuril Prednisolone Trilostane Tylosin
2	There is no marketed FDA-approved animal or human drug that could be used in an extra label manner under section 512(a)(4) or (a)(5) of the FD&C Act and par 530 to treat the condition;	Aminophylline Calcitriol Chlorambucil Cyclophosphamide Dantrolene Sodium Desmopressin Fluconazole	Ketoconazole Lomustine Penicillamine Piroxicam Prazosin Theophylline Ursodiol Zonisamide
3	The drug cannot be compounded from a legally marketed FDA-approved, conditionally approved, or indexed animal or human drug;		
4	Immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and	Diethylstilbestrol	
5	FDA has not identified a significant safety concern specific to the use of the bulk drug substance to compound animal drugs (under the listed conditions and limitations).	Unclear. May eliminate all aseptic and hazardous drugs	
	Of the most common requests, two active pharmaceutical ingredients pass the first five hurdles to be considered for nomination. FDA requires additional hurdles at submission including the provision of rigid compounding parameters, and significant data, studies and references.	Aminopentamide Demecarium Bromide	

These hurdles leave 36 of the 38 most commonly requested and generally accepted as safe items as ineligible for nomination to the positive list. All are ordered by veterinarians based on similar medical rationale : There is an FDA backorder or discontinuation, lower strength and volume are required, a higher strength is required, the patient is a compliance challenge and requires an alteration in dosage form or flavoring, the patient is sensitive to an ingredient in the FDA-approved alternative, when available.

*FDA GFI #256 Positive List nomination hurdles February 6, 2020

Background

FDA's draft Guidance for industry #256, "Compounding Animal Drugs from Bulk Substances, is based on FDA's unsupported position that the state-regulated practice of compounding pharmacy, specifically prescription compounding, is subject to federal regulation under the Food, Drug, and Cosmetic Act (FDCA). FDA continues to assert this position, despite the fact that, in 2011, a Federal court ruled that the FDCA does *not* give FDA jurisdiction over compounding pharmacy.

Nonetheless, FDA bases this new attempt to regulate compounding for animal patients on this foundation. Inexplicably, to use bulk ingredients to compound for *human* health, FDA's guidance states that the active pharmaceutical ingredient (API) *must* be contained in an FDA-approved drug or have a United States Pharmacopeia (USP) monograph. But for *animal* health, this new guidance *prohibits* compounding from the API of any drug that *is* contained in an FDA-approved human or animal drug!

In this new guidance, FDA sets conditions that are so onerous as to virtually eliminate compounding drugs for animals using bulk ingredients and requires that most compounded drugs be made from finished pharmaceutical goods such as pills and capsules, a scientifically unsound method, which would increase compounding costs by an *average* of 300%.

The Impact of the Positive List is All Negative

Perhaps, the worst of these conditions is that any bulk ingredient used must be either included on FDA's "List of Bulk Drug Substances for Compounding for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals," or include documentation of the veterinarian's medical rationale and the pharmacy's rationale as to why the medication cannot be prepared from an FDA-approved finished good. The FDA has no statutory authority to require this so-called "Positive List" or to require state-licensed professionals to justify their decisions to FDA.

The positive list currently includes only seven of the more than 450 bulk ingredients commonly prepared using bulk ingredients. But FDA assures those concerned *there's a process* for adding bulk ingredients to the list and, it says, veterinary organizations surely will step-up to do so. Many veterinarians, who have not *looked* at the process, have the very wrong impression that they can simply ask for ingredients to be added to the list and it will be done. **Nothing could be further from the truth! In fact, FDA's process is so cumbersome and restrictive that only a few additional items, if any, would be eligible for nomination, and it is possible that no additional bulk ingredients would be added by FDA to this list. Here is why:**

In addition to the positive list, FDA also released "Nominated Bulk Drug Substances That May NOT Be Used to Compound Office Stock Drugs or Antidotes for Use in Animals," (the "Negative List") which currently includes 11 bulk drug substances commonly used in compounding animal drugs. Even though many of these substances have been used by veterinarians for more than 20 years, FDA disqualifies them, claiming that FDA-approved human or animal products can be used as starting material. In so doing, FDA disregards such issues as the quantity of finished product needed (in the case of Dexamethasone or Enrofloxacin this could be hundreds of tablets); the size of the finished compound (in the case of Budesonide or Gabapentin, a compounded capsule may be 5 times larger than a compounded tablet); and the appropriateness of the finished product for use as a starting material (in the case of Itraconazole, FDA-approved finished product is a cyclodextran coated bead that could not possibly be used to make an eye drop or ointment). Other instances (Chloramphenicol, Idoxuridine) override years of veterinarians' diagnostic and therapeutic experience by stating that a different drug should be used initially, and only upon failure can the veterinarian prescribe the desired treatment.

Ultimately, the "Negative List" demonstrates that GFI #256 **prohibits compounding using any API that also is contained in an FDA-approved human or animal drug.** To nominate a drug to the positive list, it

must *not* be a component of any FDA-approved drug, and no other approved drug can be used to treat the indication. Doxycycline, for example, is prohibited because it is an approved human drug. **This restriction eliminates virtually every common medication that compounding pharmacies prepare for veterinarians!** These include amlodipine, budesonide, buprenorphine, chlorambucil, desmopressin, enrofloxacin, fluconazole, fluoxetine, gabapentin, ketoconazole, lomustine, methimazole, penicillamine, pentosan, phenylbutazone, piroxicam, prazosin, prednisolone, sildenafil, theophylline, trilostane, tylosin, ursodiol, zonisamide, and more.

The APIs on the current positive list are very narrowly defined by FDA in terms of strengths, dosage forms, species, and indications. Therefore, many frequently used compounded medications would no longer be available to veterinarians and the pets in their care. This chart shows medications that are currently offered in the formulary of one large animal-health compounding pharmacy that could no longer be offered if the FDA's new guidance were to be issued.

Medication on FDA's currently proposed positive list.	Strengths[1] Not Approved	Dosage Forms[2] Not Approved	Species[3] Not Approved	Indications[4] Not Approved
Apomorphine	6	1		
Cisapride	42	5	9	3
Guaifenesin	16	3	1	1
Miconazole Nitrate	20	3	1	1
Potassium Bromide	137	3		
Tacrolimus	12	8	1	10
Metronidazole benzoate	82	10	10	10

This proposed nomination process is extremely onerous, and nearly identical to the one for human health that began in 2015 as part of the implementation of the 2013 Drug Quality and Security Act (DQSA), which does not apply to animal health. The new animal-health guidance does not give any hints as to *how* a positive list would be developed and approved. But if the progress of developing a similar positive list for human health is to be any guide, there is a 64% failure rate of FDA adding common ingredients to the human health positive list.

Of the 740 substances that were nominated for the human-health positive list, 275 were accepted immediately because the ingredient was a component of an FDA-approved drug, leaving 465 for review. As of September 2018, only 53 substances were reviewed by the FDAs Pharmacy Compounding Advisory Committee (PCAC). There were no PCAC meetings in 2019. Of the substances reviewed—just 11% of those awaiting review—34 (64%) were rejected and 19 (36%) were approved. The first PCAC meeting was in February 2015, so this process in human health is now five years old. The veterinary guidance, GFI #256, does not refer to PCAC, nor does FDA have legislative authority to form an advisory committee for veterinary compounding, so *how* FDA would evaluate and decide on a positive list for veterinary health is unknown. One major difference here that you may have noted is that in human

[1] Strengths available from one compounding pharmacy's active formulary
[2] Dosage forms available from one compounding pharmacy's active formulary
[3] Species with which medication can be used from Plumb's Veterinary Drugs handbook
[4] Indicated uses from Plumb's Veterinary Drugs handbook

health, if the bulk ingredient is a component of an FDA-approved drug or has a USP monograph, it was automatically added to the positive list. In animal health, it is the exact opposite and worse: components of approved drugs or where there is any human or animal approved drug to treat the indication are *ineligible* for nomination.

For "outsourcing facilities," a type of organization established by the DQSA in which companies "volunteer" to be regulated directly by FDA and produce medications for human health, the record of approving APIs for the positive list is abysmal: *none* of 1,500 proposed substances have been approved—two *have* been rejected. Under FDA's "interim guidance," outsourcing facilities may compound from a list of 261 substances. But ultimately, these entities will be allowed to compound only from APIs on the Outsourcing Facility-specific positive list.

Summary

There's nothing positive for veterinarians, pet owners, or animal patients in FDA's proposed "positive list" of active pharmaceutical ingredients that may be used in compounding for animal health. FDA says it will improve access to compounded medications in animal health when in fact the complete opposite is true. FDA's proposed process for nominating APIs for the positive list is onerous and almost no medications currently compounded for animal use would be allowable because of other restrictions placed on dose, dosage form, indications, and species.

Most currently used APIs are not eligible for nomination to the positive list. In this proposed guidance, for which FDA has no statutory authority, FDA is attempting to replicate the process for FDA approval of manufactured drugs, failing to take into consideration that pharmacies are not manufacturers and are serving different needs than manufactured drugs. Animal patients cannot afford to wait for an FDA approval process to determine if their prescription can be filled for their specific drug, dosage form, species, and indication.

The outcomes for FDA's positive list will be dramatic reductions in the availability of compounded medications, complete disruption of well-established standards of care, skyrocketing costs, and animal suffering and death.

Appendix

FDA's Proposed Positive List Nomination Process

When Will FDA Include a Bulk Drug Substance on the List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals?

FDA intends to include a bulk drug substance on the List when:

1. There is no marketed FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the condition;
2. There is no marketed FDA-approved animal or human drug that could be used in an extralabel manner under section 512(a)(4) or (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition;
3. The drug cannot be compounded from a marketed FDA-approved animal or human drug consistent with 21 CFR part 530;
4. Immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and
5. FDA has not identified a significant safety concern specific to use of the bulk drug substance in animals.

For bulk drug substances used to compound drugs intended for use as antidotes in food-producing animals, in addition to 1-5 above:

6. There is sufficient scientific information for the veterinarian to determine appropriate withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).

How do I submit a nomination for the List?

You may submit nominations and comments to the docket through https://www.regulations.gov. The information to support nominations can be uploaded as attachments to your comment. The Docket No. is FDA-2018-N-4626. You may submit written submissions to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All submissions must include the Docket No. FDA-2018-N-4626 for "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals."

What information should I submit with the nomination?

You may nominate specific bulk drug substances for inclusion on the List. Each bulk drug substance should be submitted to the docket as its own, separate nomination. Submissions to the docket containing more than one bulk drug substance will not be considered an adequate nomination and will not be reviewed. In addition, nominations will only be evaluated if they are for specific active ingredients that meet the definition of a bulk drug substance. Nominated substances that do not meet this definition will not be evaluated for inclusion on the List.

For FDA to evaluate a bulk drug substance for inclusion on the List, you should submit the following information about the bulk drug substance and the compounded animal drug in the nomination:

1. Confirmation That the Nominated Substance is a Bulk Drug Substance:
    a. A statement that the nominated substance meets the definition of bulk drug substance.
2. Description of the Nominated Bulk Drug Substance:
    a. chemical name(s);
    b. common name(s);
    c. chemical grade (e.g., USP-NF, ACS, etc.);
    d. description of the strength, stability, purity; and
    e. how the nominated bulk drug substance is supplied (e.g., powder, liquid).
3. Description of the Animal Drugs That Will be Compounded with the Nominated Bulk Drug Substance:
    a. dosage form(s) into which the nominated bulk drug substance will be compounded (e.g., capsule, tablet, suspension),
    b. strength(s) of the compounded drug(s), and
    c. intended route(s) of administration of the compounded drug(s).
4. Information Requested for FDA to Evaluate Nominated Bulk Drug Substances for Inclusion on the List:
    a. The species and condition(s) that the drug to be compounded with the nominated bulk drug substance is intended to treat;

b. A bibliography of scientific literature containing safety and effectiveness data for the drug compounded using the nominated bulk drug substance;

c. A list of animal drugs, if any, that are FDA-approved, conditionally approved, or indexed for the condition(s) in the species that the drug compounded with the nominated bulk drug substance is intended to address;

d. If there are marketed FDA-approved, conditionally approved, or indexed drugs that address the same condition(s) in the same species, an explanation, supported by relevant scientific literature or other evidence, of why a compounded drug is necessary (e.g., why the FDA-approved drug is not suitable for a particular animal population);

e. Confirmation, using supporting evidence, that there are no marketed FDA-approved animal or human drugs that could be prescribed in an extralabel manner under section 512(a)(4) and (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition(s) in the species that the drug compounded with the nominated bulk drug substance is intended to address;

f. If the nominated bulk drug substance is an active ingredient in a marketed FDA-approved animal or human drug, an explanation, supported by appropriate scientific data or information, of why the animal drug cannot be compounded from the marketed FDA-approved animal or human drug under 21 CFR 530.13(b);

g. An explanation, supported by relevant scientific literature or other evidence, of why the animal drug to be compounded with the nominated bulk drug substance must be available to the veterinarian for immediate treatment to avoid animal suffering or death. Nominations should include specific information documenting that 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; and

h. A description of any human user or animal safety concerns associated with use of the nominated bulk drug substance or finished compounded drug for the condition(s) in the species that the compounded drug is intended to address. If there are concerns, an explanation, supported by scientific literature or other evidence, of why the concerns should not preclude inclusion of that nominated bulk drug substance on the List.

i. For compounded drugs intended for use as antidotes to treat toxicoses in food-producing animals, relevant scientific literature or other evidence that demonstrates that the prescribing veterinarian has a basis for determining appropriate withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).