Are All Human Drugs Actually Animal Drugs Waiting to Be Developed? What it Takes to Develop a New Animal Drug and Other Animal Health Product Considerations

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Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

July 2016
Compounding and Related Documents

Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

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Guidance for Industry[1]

Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed in the title page.

I. INTRODUCTION AND SCOPE

To qualify for exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product, among other conditions. This guidance sets forth the FDA's policies regarding this provision of section 503A, including the terms *commercially available*, *essentially a copy of a commercially available drug product*, and *regularly or in inordinate amounts*.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] This guidance does not apply to drugs compounded for use in animals, to biological products subject to licensure in a biologics license application, or to repackaged drug products. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance, *Compounding Animal Drugs from Bulk Drug Substances*. For proposed policies pertaining to mixing, diluting, and repackaging biological products, see FDA's draft guidance, *Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application.* For proposed policies pertaining to repackaged drug products, see FDA's draft guidance, *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

A. Section 503A of the FD&C Act

Section 503A, added to the FD&C Act by the Food and Drug Administration Modernization Act in 1997 and amended by the Drug Quality and Security Act in 2013, describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from the following three sections of the FD&C Act[3]:

- Section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements)
- Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use)
- Section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs))

One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503A of the FD&C Act is that it must be compounded by a licensed pharmacist or a licensed physician that "does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product."[4]

The statute further states that "[t]he term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug."[5]

A complete list of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A appears in the FDA's guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

B. Compounding, Generally

Compounded drug products serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, an elderly patient who cannot swallow a pill and needs a medicine in a liquid form that is not otherwise available, or a child who needs a drug in a strength that is lower than that of the commercially available product. Drug products for identified individual patients can be compounded by licensed pharmacists in state-licensed

[3] In addition, under section 581(13) of the FD&C Act, the term "product," for purposes of pharmaceutical supply chain security requirements, does not include a drug compounded in compliance with section 503A.

[4] See section 503A(b)(1)(D).

[5] See section 503A(b)(2).

pharmacies and Federal facilities and by licensed physicians operating under section 503A of the FD&C Act. Drug products can also be compounded by outsourcing facilities under section 503B of the FD&C Act for identified individual patients pursuant to prescriptions or for distribution to health care practitioners without first receiving a prescription.[6] Both sections 503A and 503B restrict compounding drug products that are essentially a copy of a commercially available drug product (section 503A) or an approved drug product (section 503B).

C. Risks Associated with Compounded Drug Products

Although compounded drugs can serve an important need, they also pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, licensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements. Furthermore, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products that they compound because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of a serious adverse event or visible contamination.

FDA has investigated numerous serious adverse events associated with compounded drug products that were contaminated or otherwise compounded improperly, including the adverse events associated with the 2012 fungal meningitis outbreak in which contaminated injectable drug products resulted in more than 60 deaths and 750 cases of infection. FDA has also identified many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health and that shipped the compounded drug products made under these conditions to patients and health care practitioners across the country, sometimes in large amounts.

D. Compounded Drugs That Are Essentially Copies of Commercially Available Drug Products

Section 503A provides exemptions from new drug approval, labeling with adequate directions for use, and CGMP requirements of the FD&C Act, so that drug products can be compounded as customized therapies for identified individual patients whose medical needs cannot be met by commercially available drug products. The restrictions on making drugs that are essentially copies ensure that pharmacists and physicians do not compound drug products under the exemptions for patients who could use a commercially available drug product. Such a practice would create significant public health risks because patients would be unnecessarily exposed to

[6] Section 503B of the FD&C Act describes the conditions that must be met for a human drug product compounded by an outsourcing facility to qualify for exemptions from sections 505, 502(f)(1), and 582 (concerning drug supply chain security requirements) of the FD&C Act. The conditions applicable to outsourcing facilities are discussed in separate guidances applicable to those facilities.

drug products that have not been shown to be safe and effective and that may have been prepared under substandard manufacturing conditions. FDA has investigated serious adverse events in patients who received contaminated compounded drugs when a comparable approved drug, made in a facility subject to CGMP requirements, was available.

In addition to these immediate public health risks, section 503A's limitations on producing a drug product that is essentially a copy of a commercially available drug product protects the integrity and effectiveness of the new drug and abbreviated new drug approval processes that Congress put in place to protect patients from unsafe, ineffective, or poor quality drugs. Furthermore, sponsors may be less likely to invest in and seek approval of innovative, life-saving medications if a compounder could, after a drug is approved, compound "substitutes" that have not had to demonstrate safety and effectiveness and are not produced in accordance with CGMP requirements or labeled with adequate directions for use.

Sponsors might also be less likely to seek approval of an ANDA for a generic drug if compounders were permitted to compound drugs that are essentially copies of commercially available drugs without going through the ANDA process. An ANDA must include data to demonstrate that the drug has the same active ingredient and is bioequivalent to an approved drug. FDA also conducts a premarketing inspection of proposed manufacturing facilities before approving the application.

The copies restriction also protects FDA's drug monograph process. FDA has an ongoing process for evaluating the safety and effectiveness of certain over-the-counter (OTC) medications, and if the Agency determines that an OTC drug meets certain conditions and is generally recognized as safe and effective, it will publish a final monograph specifying those conditions. Products that comply with a final monograph may be marketed, but manufacturers are required to meet CGMP standards. Restrictions in section 503A prevent compounders from producing drugs without having to comply with monograph standards, or CGMP requirements.

III. POLICY

As stated above, to qualify for the exemptions under section 503A of the FD&C Act, a drug must be compounded by a licensed pharmacist or a licensed physician that does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.[7] In other words, a compounded drug product is not eligible for the exemptions in section 503A if it is both 1) essentially a copy of a commercially available drug product, and it is 2) compounded regularly or in inordinate amounts. Accordingly, and as discussed below, when evaluating whether a drug product meets the condition in section 503A regarding essentially copies, FDA intends to determine first whether a compounded drug product is *essentially a copy of a commercially available drug product*, and if it is, FDA intends to determine second whether the drug product was compounded regularly or in inordinate amounts.

[7] See section 503A(b)(1)(D).

FDA's policies with regard to the terms (1) *commercially available drug product*, (2) *essentially a copy of a commercially available drug product*, and (3) *regularly or in inordinate amounts*, are as follows:

A. Commercially Available Drug Product

For purposes of this guidance, a drug product is commercially available if it is a marketed drug product.

We do not consider a drug product to be commercially available if

- the drug product has been discontinued and is no longer marketed[8]) or
- the drug product appears on the FDA drug shortage list in effect under section 506E of the FD&C Act.[9] A drug "appears on the drug shortage list in effect under section 506E" if the drug is in "currently in shortage" status (and not in "resolved" status) in FDA's drug shortage database.

Commercially available drugs are available on the market, and they are generally subject to FD&C Act requirements relating to approval, labeling, and CGMP requirements, and the copies restriction applies to all such drugs because section 503A is not intended to provide a means for compounders to produce compounded drugs exempt from the Act's requirements that are essentially copies of commercially available drug products.

B. Essentially a Copy of a Commercially Available Drug Product

1. What is Essentially a Copy?

FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if:

- the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available drug product;
- the API(s) have the same, similar, or an easily substitutable dosage strength; and
- the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug,

[8] FDA maintains a list of approved drug products that sponsors have indicated are not marketed in the discontinued section of the list of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). See http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Specifically, the list includes approved drug products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn for safety or effectiveness reasons, or have had their approvals withdrawn for reasons other than safety or effectiveness subsequent to being discontinued from marketing.

[9] See http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

unless a prescriber determines that there is a change, made for an identified individual patient, which produces for that patient a significant difference from the commercially available drug product.

The limitations in section 503A(b)(1)(D) apply to the compounding of drug products that are *essentially* copies of a commercially available drug product – not only to drugs that are exact copies or even to drugs that are nearly identical. This is to ensure that compounders do not evade the limits in this section by making relatively small changes to a compounded drug product and then offering the drug to the general public without regard to whether a prescribing practitioner has determined that the change produces for the patient a significant difference. For example, Congress contemplated that a compounded drug may be essentially a copy of a commercially available drug if "minor changes in strength (such as from .08% to .09%) are made that are not known to be significant . . ." for the patient for whom the drug was prescribed.[10]

a. Same API

With regard to the characteristics listed above, an API is the substance in a drug product that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body.[11] When a compounded drug product offers the same API as a commercially available drug product, in the same, similar, or easily substitutable dosage strength and for use through the same route of administration, we generally intend to consider such a drug product *essentially a copy,* unless a prescriber determines that there is a change, made for an individual patient, that will produce a significant difference for that patient.

We recognize that, for some patients, a drug product that has the same API, strength, and route of administration may include a change that produces a significant difference for a particular patient. For example, a drug product compounded without a particular inactive ingredient may produce a significant difference for a patient who has an allergy to the inactive ingredient in the commercially available drug product. However, for other patients, this change may produce no difference at all. Congress did not intend for compounders to use, for example, the fact that some patients may have allergies as a basis to compound a drug without the inactive ingredient for other patients who do not have the allergy under the exemptions in section 503A (i.e., without meeting requirements for premarket approval, labeling with adequate directions for use, or CGMP requirements).[12] In the context of compounding and consistent with the statute, we intend to consider such a drug essentially a

[10] U.S. House. Food and Drug Administration Modernization Act of 1997*, Conference Report* (to Accompany S. 830). (105 H. Rpt. 399).

[11] Section 503A refers to bulk drug substances. A *bulk drug substance* is defined as any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances (21 CFR 207.3(4)).

[12] *See* note 10.

copy, unless a prescriber determines that there is a change that will produce a significant difference for the patient for whom it is prescribed.

b. Same, Similar or Easily Substitutable Strength

FDA generally intends to consider two drugs to have a similar dosage strength if the dosage strength of the compounded drug is within 10% of the dosage strength of the commercially available drug product.

With regard to the concept of easily substitutable strength, in some cases, the same or similar dosage strength can be achieved by administration of fractional or multiple doses of a drug product. For example, if FDA-approved Drug X tablets have a dosage strength of 25 mg and a patient needs 50 mg of Drug X, FDA would generally consider a compounded Drug X 50 mg tablet to have an easily substitutable strength because the patient could take two Drug X 25 mg tablets to achieve the required dose.

c. Same Route of Administration

Route of administration is a way of administering a drug to a site in a patient (e.g., topical, intravenous, oral).[13] In general, FDA does not intend to consider a compounded drug product with the same API and similar or easily substitutable strength to be essentially a copy of a commercially available drug product if the compounded drug product and the commercially available drug product have different routes of administration (e.g., if the commercially available drug product is oral and the compounded drug product is topical). However, if the compounded drug product has the same API and similar or easily substitutable strength as the commercially available drug product and the commercially available drug product can be used (regardless of how it is labeled) by the route of administration prescribed for the compounded drug, FDA generally intends to consider the compounded drug to be essentially a copy of the commercially available drug. In this case, the compounded drug product generally would not produce a significant difference for an identified individual patient relative to the commercially available drug product.

For example, if the commercially available drug is an injectable drug sold in a vial that is labeled for intra-muscular use, but the drug also can be drawn from the vial by a smaller needle for subcutaneous administration, a compounded drug product with the same API and similar or easily substitutable strength prescribed for sub-cutaneous administration would generally be considered to be essentially a copy, unless the prescriber documents on the prescription that the compounded drug product produces a significant difference for the identified individual patient.

Same Characteristics as Two or More Commercially Available Drug Products

[13] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071667.htm.

FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if the compounded drug product contains the same APIs as two or more commercially available drug products in the same, similar, or easily substitutable strength and if the compounded drug product and the commercially available drug products have the same route of administration, unless there is documentation as described in section III.B.2. Such drug products present the same kinds of concerns as drug products that have a single API and in some respects may be more dangerous because of the potential for unintended drug interactions. For example, if drug X and drug Y are commercially available oral drug products, FDA intends to consider a compounded oral drug product that combines drug X and drug Y in strengths that are within 10% of the strengths of the respective commercially available products to be essentially a copy of the commercially available drug product, unless a prescriber determination of a significant difference has been documented.

2. Statement of Significant Difference

Pursuant to section 503A(b)(2) of the FD&C Act, a compounded drug product is not essentially a copy of a commercially available drug product if a change is made for an identified individual patient, and the prescribing practitioner has determined that the change will produce a significant difference for that patient. If a compounder intends to rely on such a determination to establish that a compounded drug is not essentially a copy of a commercially available drug product, the compounder should ensure that the determination is documented on the prescription.

FDA does not believe that a particular format is needed to document the determination, provided that the prescription makes clear that the prescriber identified the relevant change and the significant difference produced for the patient. For example, the following would be sufficient:

- "No Dye X, patient allergy" (if the comparable drug contains the dye)
- "Liquid form, patient can't swallow tablet" (if the comparable drug is a tablet)
- "6 mg, patient needs higher dose" (if the comparable drug is only available in 5 mg dose)

However, if a prescription identifies only a patient name and drug product formulation, this would not be sufficient to establish that the prescriber made the determination described by section 503A(b)(2). Note also that the significant benefit that the prescriber identifies must be produced by the change the compounder will make to a commercially available drug product (i.e., a change in drug product formulation). Other factors, such as a lower price, are not sufficient to establish that the compounded drug product is not essentially a copy of the commercially available drug product.[14]

[14] Congress noted that "where it is readily apparent, based on the circumstances, that the 'significant difference' is a mere pretext to allow compounding of products that are essentially copies of commercially available products, such compounding would be considered copying of commercially available products and would not qualify for the compounding exemptions if it is done regularly or in inordinate amounts. Such circumstances may include, for example, minor changes in strength (such as from .08% to .09%) are made that are not known to be significant or instances in which the prescribing physician is receiving financial remuneration or other incentives to write

If a prescription does not make clear that the prescriber made the determination required by section 503A(b)(2), or a compounded drug is substituted for the commercially available drug product, the compounder can contact the prescriber and if the prescriber confirms it, make a notation on the prescription that the compounded drug product contains a change that makes a significant difference for the patient. The notations should be as specific as those described above, and the date of the conversation with the prescriber should be included on the prescription.

It is not possible to offer comprehensive guidance about when a difference will be "significant" to an identified individual patient. FDA generally does not intend to question prescriber determinations that are documented in a prescription or notation. However, we do intend to consider whether a prescription or notation relied upon by a compounder to establish that a drug is not essentially a copy documents that the determination was made.

3. Documentation of shortage

If the drug was compounded because the approved drug product was not commercially available because it was on the FDA drug shortage list, the prescriber or compounder should include a notation on the prescription that it was on the drug shortage list and the date the list was checked.

4. Regularly or in Inordinate Amounts

A drug product is not eligible for the exemptions in section 503A if it is prepared by a pharmacist or physician who compounds "regularly or in inordinate amounts (as defined by the Secretary)" any drug products that are essentially copies of a commercially available drug product.[15] FDA interprets this to mean that to be compounded in accordance with section 503A, a drug product that is essentially a copy of a commercially available drug product cannot be compounded regularly – i.e., it cannot be compounded at regular times or intervals, usually, or very often. Nor can the amounts compounded be inordinate, in light of the purpose of section 503A.

Section 503A is intended to protect patients from the public health risks of providing compounded drugs to patients whose medical needs could be met by commercially available drug products and to protect the integrity and efficiency of the drug approval process. Under the statutory scheme, only very rarely should a compounded drug product that is essentially a copy of a commercially available drug product be offered to a patient. For example, a compounded drug product that has the same API, dosage strength, and route of administration as a drug product on FDA's shortage list would not be considered essentially a copy of a commercially available drug because a drug product is not considered *commercially available* if it is on FDA's drug shortage list. In addition, a compounded drug product is not essentially a copy of a

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prescriptions for compounded products." *See* the U.S. House. Food and Drug Administration Modernization Act of 1997*, Conference Report* (to Accompany S. 830). (105 H. Rpt. 399).

[15] See section 503A(b)(1)(D).

commercially available drug product if a prescriber has determined that the compounded drug has a change that produces a significant difference for a patient. We conclude, therefore, that a drug product that is essentially a copy of a commercially available drug product is compounded regularly or in inordinate amounts if it is compounded more frequently than needed to address unanticipated, emergency circumstances or in more than the small quantities needed to address unanticipated, emergency circumstances.

Once it has been determined that a compounded drug is essentially a copy of a commercially available drug product as described above, the following are examples of factors that may be the basis for concluding that it has been compounded regularly or in inordinate amounts:

- The compounded drug product amounts to more than a small number of prescriptions or a small percentage of the compounded drug products that a physician or prescriber prepares or provides to patients.
- The compounder routinely substitutes compounded drugs that are essentially copies of commercially available drugs upon receiving prescriptions for patients.
- The compounder offers pre-printed prescription pads that a prescriber can use to write a prescription for the drug product that is essentially a copy without making a determination that there is a change that will produce a significant difference for a patient.
- The compounded drug product is not compounded on an as-needed basis, but on a routine or pre-set schedule.

The foregoing list is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case.

To focus enforcement on the most significant cases, as a matter of policy, at this time FDA does not intend to take action against a compounder for compounding a drug product that is essentially a copy of a commercially available drug product regularly or in inordinate amounts if the compounder fills four or fewer prescriptions for the relevant compounded drug product in a calendar month.[16] Be aware that a prescription would not be considered to be for a drug that is essentially a copy of a commercially available drug product and would not be counted towards the four prescriptions if the prescription documents that the compounded drug product makes a significant difference for the patient as described above.

5. Recordkeeping

A licensed pharmacist or physician seeking to compound a drug product under section 503A should maintain records to demonstrate compliance with section 503A(b)(1)(D). For example, records should be kept of notations on prescriptions for identified individual patients that a prescriber has determined that the compounded drug has a change that produces a significant difference for the identified patient.

[16] For purposes of this policy, a prescription does not include additional refills. FDA intends to consider each refill of a prescription as an additional prescription.

Compounders under section 503A should also maintain records of the frequency in which they have compounded drug products that are essentially copies of commercially available drug products and the number of prescriptions that they have filled for compounded drug products that are essentially copies of commercially available drug products to document that such compounding has not been done regularly or in inordinate amounts.

#230

Guidance for Industry
Compounding Animal Drugs from Bulk Drug Substances

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Eric Nelson (CVM) at 240-402-5642, or by e-mail at eric.nelson@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]
Compounding Animal Drugs from Bulk Drug Substances

This draft guidance, when finalized, represents the Food and Drug Administration's (FDA or Agency) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this draft guidance using the contact information on the title page of this guidance.

I. INTRODUCTION AND SCOPE

This draft guidance sets forth the Food and Drug Administration's ("FDA") policy regarding compounding animal drugs from bulk drug substances[2] by state-licensed pharmacies, licensed veterinarians, and facilities that register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). This guidance reflects FDA's current thinking regarding compounding animal drugs from bulk drug substances and describes the conditions under which FDA generally does not intend to take action for violations of the following sections of the FD&C Act: section 512 (21 U.S.C. 360b), section 501(a)(5) (21 U.S.C. 351(a)(5)), section 502(f)(1) (21 U.S.C. 352 (f)(1)), and, where specified, section 501(a)(2)(B) (21 U.S.C 351(a)(2)(B)), when a state-licensed pharmacy, licensed veterinarian, or an outsourcing facility[3] compounds animal drugs from bulk drug substances.

This draft guidance only addresses the compounding of animal drugs from bulk drug substances. It does not apply to the compounding of animal drugs from approved new animal or new human drugs. Such compounding can be conducted in accordance with the provisions of section 512(a)(4) and (5) of the FD&C Act (21 U.S.C. 360b(a)(4) and (5)) and 21 CFR part 530. In addition, this draft guidance does not address the compounding of drugs intended for use in

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[1] This draft guidance has been prepared by the Center for Veterinary Medicine (CVM) in consultation with the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

[2] FDA regulations define "bulk drug substance" as "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances." 21 CFR 207.3(a)(4). "Active ingredient" is defined as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." 21 CFR 210.3(b)(7). Any component other than an active ingredient is an "inactive ingredient." See 21 CFR 210.3(b)(8). Inactive ingredients used in compounded drug products commonly include flavorings, dyes, diluents, or other excipients.

[3] "Outsourcing facility" refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act. See draft guidance for industry *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434171.pdf.

humans, which is addressed in other guidances.[4] Further, the draft guidance does not address new animal drugs for investigational use. See 21 CFR part 511.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Regulatory Framework

To be legally marketed, new animal drugs must be approved under section 512 of the FD&C Act, conditionally approved under section 571 of the FD&C Act (21 U.S.C. 360ccc), or included on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species under section 572 of the FD&C Act (21 U.S.C. 360ccc-1). The FD&C Act does not generally distinguish between compounding and other methods of animal drug manufacturing. Animal drugs that are not approved or indexed are considered "unsafe" under section 512(a)(1) of the FD&C and adulterated under section 501(a)(5) of the FD&C Act.

Although sections 503A (21 U.S.C. 353a) and 503B of the FD&C Act provide certain statutory exemptions for compounded human drugs, these sections do not provide exemptions for drugs compounded for animal use. The compounding of an animal drug from bulk drug substances results in a new animal drug that must comply with the FD&C Act's approval/indexing requirements.[5] Further, all animal drugs are required to, among other things, be made in accordance with current good manufacturing practice (cGMP) requirements (section 501(a)(2)(B)) of the FD&C Act and 21 CFR parts 210 and 211) and have adequate directions for use (section 502(f)(1) of the FD&C Act).

Sections 512(a)(4) and (5) of the FD&C Act provide a limited exemption from certain requirements for compounded animal drugs made from already approved animal or human drugs. Such use is considered an extralabel use and the FD&C Act provides an exemption from the approval requirements and requirements of section 502(f) of the FD&C Act for extralabel uses that meet the conditions set out in the statute and FDA regulations at 21 CFR part 530. Among other things, these regulations specify that nothing in the regulations should be construed as permitting compounding animal drugs from bulk drug substances.

In 1996, FDA announced the availability of a CPG (section 608.400) entitled, "Compounding of Drugs for Use in Animals" (61 FR 34849, July 3, 1996), to provide guidance to FDA's field and headquarters staff with regard to the compounding of animal drugs by veterinarians and pharmacists. An updated CPG was made available on July 14, 2003 (68 FR 41591). This draft guidance supersedes that CPG, which has now been withdrawn.

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[4] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm.

[5] See *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383, 394 (5th Cir. 2008).

B. Compounding Animal Drugs

Numerous drugs are approved or indexed for use in animals. However, there are many different species of animals with different diseases and conditions for which there are no approved or indexed animal drugs. In some cases, approved human drugs can be used to treat an animal under the extralabel use provisions of the FD&C Act and FDA regulations (sections 512(a)(4) and (a)(5) of FD&C Act and 21 CFR part 530). For example, various chemotherapeutic drugs approved for humans are used to treat cancer in dogs and cats. FDA recognizes that there are circumstances where there is no drug available to treat a particular animal with a particular condition, because either no drug is approved for a specific animal species or no drug is available under the extralabel drug use provisions. In those limited circumstances, an animal drug compounded from bulk drug substances may be an appropriate treatment option.

However, FDA is concerned about the use of animal drugs compounded from bulk drug substances, especially when approved alternatives exist that can be used as labeled or in an extralabel manner consistent with the requirements of FDA's extralabel provisions. Compounded drugs have not undergone premarket FDA review of safety, effectiveness, or manufacturing quality. The unrestricted compounding of animal drugs from bulk drug substances has the potential to compromise food safety, place animals or humans at undue risk from unsafe or ineffective treatment, and undermine the incentives to develop and submit new animal drug applications to FDA containing data and information to demonstrate that the product is safe, effective, properly manufactured, and accurately labeled.

III. POLICY

As discussed above, animal drugs are generally subject to the adulteration, misbranding, and approval provisions of the FD&C Act. Generally, FDA does not intend to take action under sections 512(a), 501(a)(5), 502(f)(1) and 501(a)(2)(B) of the FD&C Act if a state-licensed pharmacy or a licensed veterinarian compounds animal drugs from bulk drug substances in accordance with the conditions described below, and the drug is not otherwise adulterated or misbranded. In addition, FDA generally does not intend to take action under sections 512(a), 501(a)(5), and 502(f)(1) of the FD&C Act if an outsourcing facility compounds animal drugs in accordance with all of the applicable conditions described below, and the drug is not otherwise adulterated or misbranded.

FDA's decision not to take enforcement action depends on its ability to evaluate whether the compounding of animal drugs is in accordance with the conditions below. Therefore, entities compounding animal drugs should keep adequate records to demonstrate that they are compounding such drugs in accordance with all of the applicable conditions described below.

The conditions referred to above are as follows:

A. If the animal drug is compounded in a state-licensed pharmacy:

1. The drug is compounded by or under the direct supervision of a licensed pharmacist.

2. The drug is dispensed after the receipt of a valid prescription from a veterinarian for an individually identified animal patient that comes directly from the prescribing veterinarian or from the patient's owner or caretaker to the compounding pharmacy. A drug may be compounded in advance of receipt of a prescription in a quantity that does not exceed the amount of drug product that the state-licensed pharmacy compounded pursuant to patient-specific prescriptions based on a history of receipt of such patient-specific prescriptions for that drug product over any consecutive 14-day period within the previous 6 months.

3. The drug is not intended for use in food-producing animals, and the prescription or documentation accompanying the prescription for the drug contains the statement "This patient is not a food-producing animal." For purposes of this draft guidance, all cattle, swine, chicken, turkey, sheep, goats, and non-ornamental fish are always considered to be food-producing animals regardless of whether the specific animal or food from the specific animal is intended to be introduced into the human or animal food chain (e.g., pet pot-bellied pigs and pet chicks are always considered to be food-producing animals). In addition, for purposes of this draft guidance, any other animal designated on the prescription or in documentation accompanying the prescription by the veterinarian as a food-producing animal, regardless of species, is considered to be a food-producing animal (e.g., rabbits, captive elk, captive deer).

4. If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug:

    a. there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care, and
    b. the prescription or documentation accompanying the prescription contains a statement that the change between the compounded drug and the FDA-approved drug would produce a clinical difference for the individually identified animal patient. For example, the veterinarian could state that, "Compounded drug X would produce a clinical difference for the individually identified animal patient because the approved drug is too large a dose for the animal and cannot be divided or diluted into the small dose required."

5. If there is an FDA-approved animal or human drug with the same active ingredient(s), the pharmacy determines that the compounded drug cannot be made from the FDA-approved drug(s), and documents that determination.

6. The pharmacy receives from the veterinarian (either directly or through the patient's owner or caretaker), in addition to any other information required by state law, the following information, which can be documented on the prescription or documentation accompanying the prescription:

    a. Identification of the species of animal for which the drug is prescribed; and,
    b. The statement "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) or (5) and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed."

7. Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 510) and is accompanied by a valid certificate of analysis.

8. The drug is compounded in accordance with Chapters <795> and <797> of the United States Pharmacopeia and National Formulary (USP—NF)[6] (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).

9. The drug is not sold or transferred by an entity other than the entity that compounded such drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care.

10. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the pharmacy reports it to FDA on Form FDA 1932a. Form FDA 1932a can be downloaded at http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf.

11. The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient and the name of the owner or caretaker of the animal patient.

B. If the animal drug is compounded by a licensed veterinarian:

1. The drug is compounded and dispensed by the veterinarian to treat an individually identified animal patient under his or her care.

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[6] Chapters <795> *Pharmaceutical Compounding—Nonsterile Preparations* and <797> *Pharmaceutical Compounding—Sterile Preparations* can be found in the combined *United States Pharmacopeia and National Formulary (USP-NF)*, available at http://www.usp.org.

2. The drug is not intended for use in food-producing animals as defined in section III.A.3 of this guidance.

3. If the drug contains a bulk drug substance that is a component of any marketed FDA-approved animal or human drug, there is a change between the compounded drug and the comparable FDA-approved animal or human drug made for an individually identified animal patient that produces a clinical difference for that individually identified animal patient, as determined by the veterinarian prescribing the compounded drug for his/her patient under his/her care.

4. There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under sections 512(a)(4) and (5) of the FD&C Act and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which the drug is being prescribed.

5. The drug is compounded in accordance with USP—NF Chapters <795> and <797> (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).

6. Any bulk drug substance used is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis.

7. The drug is not sold or transferred by the veterinarian compounding the drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by the veterinarian to a patient under his or her care, or the dispensing of an animal drug compounded by the veterinarian to the owner or caretaker of an animal under his or her care.

8. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs the veterinarian compounded from bulk drug substances, he or she reports it to FDA on Form FDA 1932a. Form FDA 1932a can be downloaded at http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf.

9. The label of any compounded drug indicates the species of the intended animal patient, the name of the animal patient and the name of the owner or caretaker of the animal patient.

C. If the animal drug is compounded by an outsourcing facility:

1. The drugs are compounded only from bulk drug substances appearing on Appendix A of this draft guidance.

2. The drug is compounded by or under the direct supervision of a licensed pharmacist.

3. The drug is not intended for use in food-producing animals, as defined in Section III.A.3 of this guidance, and the prescription or order, or documentation accompanying the prescription or order, for the drug contains the statement, "This drug will not be dispensed for or administered to food-producing animals."

4. The drug is compounded in accordance with cGMP requirements.[7]

5. Any bulk drug substance used is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis.

6. The drug is not sold or transferred by an entity other than the outsourcing facility that compounded such drug. For purposes of this condition, a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care.

7. Within 15 days of becoming aware of any product defect or serious adverse event associated with animal drugs it compounded from bulk drug substances, the outsourcing facility reports it to FDA, on Form FDA1932a. Form FDA 1932a can be downloaded at http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/animaldrugforms/ucm048817.pdf.

8. All drugs compounded for animals by an outsourcing facility are included on the report required by section 503B of the FD&C Act to be submitted to the Food and Drug Administration each June and December identifying the drugs made by the outsourcing facility during the previous 6-month period, and providing the active ingredient(s); source of the active ingredient(s); NDC number of the source ingredient(s), if available; strength of the active ingredient(s) per unit; the dosage form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.[8] The outsourcing facility should identify which reported drugs were intended for animal use.

9. The veterinarian's prescription or order states that the drug is intended to treat the species and condition(s) for which the substance is listed in Appendix A.

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[7] FDA intends to determine whether this condition is met by evaluating whether the facility complies with FDA regulations applicable to cGMPs for compounding of human drugs by outsourcing facilities. *See, e.g.*, draft guidance for industry, *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (July 2014), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf

[8] FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (November 2014), which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Available at http://www.fda.gov/downloads/Drugs/NewsEvents/UCM424303.pdf. Although this guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the animal drug products they compounded.

10. The label of the drug includes the following:

    a. Active ingredient(s).
    b. Dosage form, strength, and flavoring, if any.
    c. Directions for use, as provided by the veterinarian prescribing or ordering the drug.
    d. Quantity or volume, whichever is appropriate.
    e. The statement "Not for resale."
    f. The statement "For use only in [fill in species and any associated condition or limitation listed in Appendix A]."
    g. The statement "Compounded by [name of outsourcing facility]."
    h. Lot or batch number of drug.
    i. Special storage and handling instructions.
    j. Date the drug was compounded.
    k. Beyond use date (BUD) of the drug.
    l. Name of veterinarian prescribing or ordering the drug.
    m. The address and phone number of the outsourcing facility that compounded the drug.
    n. Inactive ingredients.
    o. The statement "Adverse events associated with this compounded drug should be reported to FDA on a Form FDA 1932a."
    p. If the drug is compounded pursuant to a patient specific prescription, the species of the animal patient, name of the animal patient, and name of the owner or caretaker of the animal patient.

APPENDIX A[9]

LIST OF BULK DRUG SUBSTANCES THAT MAY BE USED BY AN OUTSOURCING FACILITY TO COMPOUND DRUGS FOR USE IN ANIMALS

This Appendix, when finalized, will contain a list of bulk drug substances that may be used by facilities registered under section 503B as outsourcing facilities to compound animal drugs pursuant to a prescription from a veterinarian for an individually identified animal patient or pursuant to an order from a licensed veterinarian for veterinarian office use, and in accordance with any specified limitations or conditions.

This list will be developed with public input; the process for nominating bulk drug substances for this list is described in the Federal Register notice soliciting nominations for such bulk drug substances. FDA intends to limit the bulk drug substances in this Appendix to address situations where all of the following criteria are met:

- there is no marketed approved, conditionally approved, or index listed animal drug that can be used as labeled to treat the condition;
- there is no marketed approved animal or human drug that could be used under section 512(a)(4) or (a)(5) and 21 CFR Part 530 (addressing extralabel use of approved animal and human drugs) to treat the condition;
- the drug cannot be compounded from an approved animal or human drug;
- immediate treatment with the compounded drug is necessary to avoid animal suffering or death; and
- 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).

FDA intends to review the nominated bulk drug substances on a rolling basis and to periodically update this Appendix.

LIST:

[9] To submit nominations for this list, refer to the Federal Register notice entitled, "List of Bulk Drug Substances That May be Used by an Outsourcing Facility to Compound Drugs for Use in Animals," published May 19, 2015. After the period for nominations closes, you may petition FDA under 21 CFR 10.30 to add or remove specific listings.

January 28, 2016

Food, Drug and Cosmetic Law Section: Bulk Drug Compounding in the Animal Health Industry

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- Litigator at Axinn, Veltrop & Harkrider LLP (www.axinn.com)
- Graduated from Cornell Law School and the College of Veterinary Medicine in 2009.
- Clerked at the U.S. Attorney's Office in the Northern District of New York.
- Serving as a Director for the New York State Defenders Association.
- Experience in a variety of technologies, including: pharmaceuticals, biologics, surgical devices and techniques, medical devices, consumer products and electronics.
- Represented clients in licensing and patent disputes, contract and settlement negotiations, FDA regulatory matters, employment issues, complex commercial litigations and international disputes.
- Experience litigating disputes in federal district courts, the Federal Circuit and state courts.
- Pro bono practice has included immigration proceedings, housing court and divorces.
- Owned by two Bedlington Terriers.

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- Senior Counsel at McGuireWoods LLP (https://www.mcguirewoods.com/People/M/Brian-J-Malkin.aspx)
- Chair of the Food, Drug and Cosmetic Law Section of the New York State Bar Association
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- Has more than 22 years of food and drug law practice and over 11 years of intellectual property law practice
- His practice includes the interrelation between patent law and food and drug law.
- Brian's regulatory experience includes all types of FDA-regulated products: drugs (including animal drugs), biologics, medical devices, foods and dietary supplements, tobacco products, and cosmetics.
- Brian's intellectual property experience includes FDA and patent litigation for both innovator and generic/biosimilar companies.

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The George Washington University, BA, Economics, 1988

Rachael G. Pontikes

Panelist

- Partner at Duane Morris LLP (http://www.duanemorris.com/attorneys/rachaelgpontikes.html)
- Counsels compounding pharmacies and retail chains in the compounding industry in both human and animal health regarding compliance with various applicable state and federal law.
- Acts as litigation counsel for compounding pharmacies in disputes with the state boards of pharmacy, the Food and Drug Administration and the Drug Enforcement Administration in administrative proceedings and federal courts.
- Ms. Pontikes is a nationally recognized authority in the Drug Quality Security Act (DQSA)-Compounding Quality Act (CQA), participating in various discussions with the Senate HELP Committee staffers as the law was drafted.
- She served as trial counsel in *Medical Center v. Mukasey* through defeat of the motion to dismiss, and trial counsel and appellate counsel in *Wedgewood Village Pharmacy v. United States*.

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Wesleyan University, B.A., Philosophy and Italian Studies, with honors, 1996

Clint W. Vranian

Panelist

- Animal Health Industry Consultant
- Former General Counsel at Elanco, Novartis Animal Health
- Represented multinational pharmaceutical and animal health companies for over 15 years, both in private practice and in General Counsel roles within Novartis Animal Health and Elanco Animal Health.
- Mr. Vranian has led M&A, Business Development and commercial matters spanning all areas of the Animal Health industry, including representing the industry before the FTC in the Pet Medications Workshop of 2012.
- Most recently, Mr. Vranian led the antitrust clearance and legal integration of Elanco Animal Health's North American region following its acquisition of Novartis Animal Health.
- Mr. Vranian graduated from Emory and Henry College in 1994, received his JD from the University of Richmond in 1998, and his MBA from Duke University in 2010.

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Emory and Henry College, B.A. (Philosophy and Classical Studies), 1994

Dr. Susan Wylegala

Panelist

- Owner of the Cheektowaga Veterinary Hospital (http://www.cheektowagavet.com/our-team/veterinarians/)
- President of the New York State Veterinary Medical Society (NYSVMS)
- President of the Board of Directors of the Veterinary Emergency Clinic in Buffalo, NY
- Past President of the Western New York Veterinary Medical Association and has received two Regional Merit Awards from the WNYVMA
- She serves as co-chair of the New York State Veterinary Conference.
- Dr. Wylegala serves on the Dean's Advisory Council for the New York State College of Veterinary Medicine at Cornell.
- She is a regular guest on A.M. Buffalo's "Pet Talk" segment [WKBW Channel 7, Buffalo, NY].
- Dr. Wylegala has 4 cats; Stella, Stasz, Leo and one who lives at the hospital named Frieda.
- While not working, she enjoys cycling, boxing and gardening. Dr. Wylegala also captains a cycling team called the "Animaniacs." Her team has participated in the "Ride for Roswell" benefitting Roswell Park Cancer Institute for over 10 years.

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Practice Areas

Small Animal Medicine

Education

Cornell University, College of Veterinary Medicine, D.V.M., 1988

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NYSBA: Animal Health Committee of the Food, Drug and Cosmetic Law Section

- 2015
  - Drafted and submitted comments on FDA Draft Guidance #230 (Compounding Animal Drugs from Bulk Drug Substances), working in cooperation with the American Veterinary Medical Association
- Agenda for 2016
  - Push FDA to draft rules specific for the filing of Abbreviated New Animal Drug Applications (ANADA)
  - Request USDA provide guidance and examples for its veterinary biologics application process
  - Request clarity and guidance on which biologics are to be under the jurisdiction of the FDA and USDA
  - Coordinate with NYSVMS on a New York legislative proposal regarding animal drug compounding

FDA's View

- The Federal Food, Drug and Cosmetic Act (FD&C Act) does not distinguish between animal compounding and animal drug manufacturing
  - FDA views animal drugs as generally "unsafe," "misbranded" and "adulterated" if not approved, conditionally approved or on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species under Section 572 of the FD&C Act.
- Section 512(a)(4) and (5) provides for exemptions for animal drug compounding from approved animal and human drugs when extralabel use requirements are met (*see* 21 C.F.R. Part 530).

FDA's View:
Part 530 Requirements for Extralabel Use

- Implements the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994
- On the lawful order of a licensed veterinarian within the context of a valid veterinary-client-patient relationship
- New animal drugs and approved new human drugs are limited to treatment modalities when the health of an animal is threatened or suffering or death may result from failure to treat.
  - No approved new animal or human drug that will, in available dosage form and concentration, treat the condition diagnosed.
- Actual use or intended use of a drug in an animal in a manner not in accordance with approved labeling.
  - Including use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

FDA Regulation and Oversight of Animal Compounding Pharmacies

- 1996 CPG 608.400 (Compounding of Drugs for Use In Animals), updated in 2003, withdrawn May 2015
  - Largely prohibited the compounding of drugs from bulk substances for both food animals and non-food animals with a few exceptions.
  - FDA generally deferred to state authorities for regulation of compounding, but where compounding raised "concerns normally associated with a drug manufacturer" and resulted in new animal drug, adulteration or misbranding violations of the FD&C Act, FDA would consider acting if, for example, the following occurred:
    - Compounding for situations where health of animal not threatened or suffering or death of animal not likely if animal not treated
    - Compounding of drugs in anticipation (i.e., in advance of receiving prescriptions)
    - Compounding of drugs prohibited for extralabel use due to public health risks
    - Compounding using commercial scale manufacturing equipment
    - Compounding where an approved animal or human drug was available and could appropriately be used to treat the condition

FDA Regulation and Oversight of Animal Compounding Pharmacies

- CPG 608.400 called into question by Franck's Lab case (*U.S. v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fla. 2011), appeal filed but later jointly dismissed as moot)
  - Franck's lab compounded animal drugs under state-regulated guidelines, including patient-client-veterinarian relationship, only for non-commercially-available drugs, and placed warnings on drugs that could not be used for non-food animals
  - FDA advanced prior position that all veterinary compounding from bulk drug substances for non-food animals as well as for food animals violated the FD&C Act
  - Court ruled that FDA did not have authority to enjoin the "long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a non-food producing animal by compounding from bulk substances"

FDA Regulation and Oversight of Animal Compounding Pharmacies

- In May 2015, FDA issued Draft Guidance #230: Compounding Animal Drugs from Bulk Drug Substances
  - Drafted to replace 1996 CPG 608.400 (Compounding of Drugs for Use In Animals)
  - Applies to state-licensed pharmacies, licensed veterinarians, and facilities that register with FDA as outsourcing facilities under § 503B of the Drug Quality and Security Act
  - FDA attempted to provide limited circumstances where it will take no enforcement action for the compounding of bulk substances
  - Covers three groups of animal drug compounders:
    - State-licensed pharmacies
    - State-licensed veterinarians
    - Outsourcing facility

FDA Draft Guidance #230: Pharmacies & Veterinarians

- Requires:
  - No FDA-approved animal or human drugs that can be used as labeled or extralabel to treat the disease, symptom, or condition for which prescribed
  - Valid Rx from veterinarian for individually-identified animal patient and can only be administered, not dispensed, by a veterinarian OR
    - Compounded, dispensed and/or administered by a veterinarian to treat individually-identified animal patient under his or her care.
  - Advance quantities possible depending on state rules for patient-specific Rx's
    - Quantities based on history of product over a consecutive 14-day period within last 6 months.
  - Not for food-producing animals (food animals include cattle, swine, chicken, turkey, sheep, goats and non-ornamental fish) and label includes such a statement.
  - If there is an approved human or animal drug with same active ingredient, prescribing veterinarian must document reason why the change would produce a clinical difference and cannot be compounded from approved drug
  - Reporting of serious adverse event within 15 days of becoming aware of the event.

FDA Draft Guidance #230: Outsourcing Facility

- Similar to animal pharmacy with the following modifications:
  - Creates a new category of animal drug compounding by an outsourcing facility, similar to provisions for human drug compounding (but there is no statutory authority for this in animals).
  - Compounding limited to the drugs listed in Appendix A
  - Drugs compounded for animals by an outsourcing facility are included in the report required by § 503B of the FD&C Act to be submitted to FDA each June and December identifying drugs made by the facility
  - Veterinarian's prescription or order states the drug is intended to treat the species and condition(s) for which the substance is listed in Appendix A
  - Certain product labeling including language such as "Not for resale," "Compounded by [name of outsourcing facility]" and "Adverse events associated with this compounded drug should be reported to FDA on Form FDA 1932a"
  - Veterinarian is only allowed to administer bulk drug compounded at an outsourcing facility

FDA Draft Guidance #230: Appendix A

- A list of bulk drug substances that entities registered as outsourcing facilities under Section 503b of the FD&C Act are limited to for purposes of compounding.
  - Compounding of an Appendix A drug allowed for an individual animal patient or veterinarian office use when that drug is listed on Appendix A for that species and condition only
  - FDA solicited input for bulk drug substances that should be on the list in Appendix A
- Comments on Draft Guidance closed November 16, 2015.

Submitted Comments

- Initial period for comments extended from August 17, 2015 to November 16, 2015.
- 160 comments submitted; 112 available on www.regulations.gov (Docket ID: FDA-2015-D-1176)
  - Individual citizens
  - Individual veterinarians
  - Veterinarian groups
  - Pharmacy groups
  - Compounding pharmacies and compounding pharmacy groups
  - Drug manufacturers

Submitted Comments: Veterinarians (Example AVMA)

- Does not consider whether FDA has the authority to issue such guidance.
- Focuses on clarifying the Guidance and the possible negative consequences of the Guidance as currently drafted on animal health and veterinarian.
  - Inability to treat herds as opposed to individual animals.
  - Inability of veterinarians to maintain a stock of commonly needed or emergency required compounded drugs.
  - Need for improved adverse event reporting system for all animal drugs, including compounded drugs.
  - Inability to get a bulk compounded drug if it does not appear on Appendix A and the implication of having such a list.

Submitted Comments: New York State Bar Association

- Collaborated with AVMA to ensure veterinary perspective on the draft guidance was understood.
- Highlighted that FDA should instead consider initiating notice and comment rulemaking to establish bulk compounding guidelines instead of the informal draft to final guidance procedure chosen.
  - Would allow for more complete engagement of both the public and the many, diverse stakeholders in animal health.
  - Would help ensure any final rule met the goals of improving safety and reliability of bulk compounded drugs while not unnecessarily limiting access to important treatment options for animals.
  - Recognized that Congress had not legislated yet on the issue of compounding bulk substances for animal health.
- Discussed issues and concerns with the current draft guidance.
  - Examples: Improved adverse event reporting system; inability of veterinarians to dispense bulk compounded drugs compounded at a pharmacy; individual patient vs. herds; etc.

Submitted Comments: Drug Manufacturers (Example Zoetis)

- Supports FDA's interest in addressing the issues of bulk drug compounding in the animal health area but finds the proposed guidance to be inadequate.
  - The "proposed guidance will foster more widespread and virtually unregulated compounding of new animal drugs."
  - Will "result in the establishment of two manufacturing standards for new animal drugs" – one for drug manufacturers and one for compounding pharmacies
  - "[G]uidance will have deleterious impact on the development of innovative new products for the animal health industry as it will reduce the incentive for investment in animal drug research and development."
  - Concerned with "loopholes" in guidance that "permit 'mimics or 'one-off knock offs' of FDA-approved products to be compounded from bulk drug substance when FDA-approved products are available to treat the disease condition."
- Compounding from bulk substances is appropriate:
  - "when the health of an animal is threatened and there are no FDA approved drugs for the attending veterinarian to use to treat the disease condition"
  - "when the approved product is no longer manufactured"

Submitted Comments: Compounding Pharmacies (Example Duane Morris)

- "[T]here is no legal authority for the positions FDA takes in the [guidance]."
  - "The FDCA does not give FDA the authority to regulate veterinary compounding." Veterinary compounding from bulk ingredients is a state-regulated practice.
  - AMDUCA does not give FDA "authority to regulate all veterinary compounding from bulk ingredients." It simply permits certain off-label uses of FDA-approved human and animal drugs in treating animals.
  - Drug Quality and Security Act (DQSA) affirmatively does not address veterinary compounding.
- "FDA does not have the authority to expansively regulate the practice of veterinary medicine."
  - Guidance dictates under what circumstances compounded drugs may be used and specific medical decisions veterinarians must make before prescribing compounded medications.
- Guidance's framework "is unworkable and will have an adverse impact on animal health."
  - Creates "unnecessary obstacles that will prohibit animals and veterinarians from obtaining necessary medication."

Government Accountability Office: Report on Drug Compounding for Animals

- Key findings:
  - Drugs compounded for animals can offer medical benefits such as serving as treatment options when no suitable drug approved by FDA is available.
  - Compounded drugs, however, can also pose risks of causing harm or being ineffective such as when they contain too much or too little of an active ingredient.
  - Extent to which drugs are compounded for animals is unknown since FDA- and state-collected information is not aggregated or comprehensive.
  - FDA does not know the extent to which compounded drugs are associated with adverse events.
  - FDA does not currently have final guidance directing its regulatory approach on drug compounding for animals.
  - FDA has not consistently documented the bases for actions it has taken to regulate bulk animal drug compounding in the past, including how or whether it followed up on these actions.

Dr. Susan Wylegala, *NYSVMS*

- The inability of a veterinarian to directly dispense a compounded medication can result in delay in treatment or treatment failure for patients who require a compounded product.
- With the limitations recommended, there are challenges in treating populations of species such as aviaries, wildlife, aquaria animals, lab animals and shelters that treat large groups of animals directly, frequently with compounded products.
- The circumstances that a veterinarian would need to have drugs compounded from a bulk substance include: The approved drug is not available, the compounded product cannot be made from the approved drug, or there is no approved drug from which to compound the preparation.
- Veterinary medicine is unique in the number of species being treated, the limitations of FDA approved veterinary drugs, and intermittent drug shortages require that veterinarians frequently (daily) utilize compounded products for the health of their patients.

Clinton Vranian,
Animal Health Industry Consultant

- The Animal Health pharmaceutical industry is committed to two things: compliance with the FD&C Act and the preservation and deference to the Veterinary Client Patient Relationship, which is the core of ensuring the health and well-being of animals.
- The guidance in and of itself can be construed to be consistent with these goals through its deference to the veterinary prescription and limited allowance on a case-by-case basis.
- Such activity has never been of concern to industry. However, our experience is that opportunistic compounders all-too-often attempt to leverage these exceptions to circumvent the approval requirements to which other manufacturers are subject.
- This impact is especially profound in animal health where generic compounds often retain value long beyond the expiration of the IP protection.
- FDA's reluctance or inability to enforce in such cases often facilitates this behavior.

Rachel Pontikes, *Duane Morris LLP*

- Compounding animal drugs, as a traditional part of pharmacy practice, is regulated by the states. States have a complex set of regulations for compounding, including quality standards, and compounds are overseen by the state board of pharmacy. Most states incorporate the uniform quality standards found in the United States Pharmacopeia (USP).
- As FDA does not have the authority to regulate compounding of animal drugs, FDA lacks authority to issue the draft Guidance For Industry, regarding compounding for use in animals.
- FDA does not have the authority to practice medicine—as such, FDA does not have the authority to place the requirements on veterinarians contemplated by the draft GFI.
- Compounding animal drugs from bulk ingredients (API) is not illegal under state law—and, the only court that has analyzed the issue (*Francks*) found FDA did not have the authority to declare compounding from bulk illegal.

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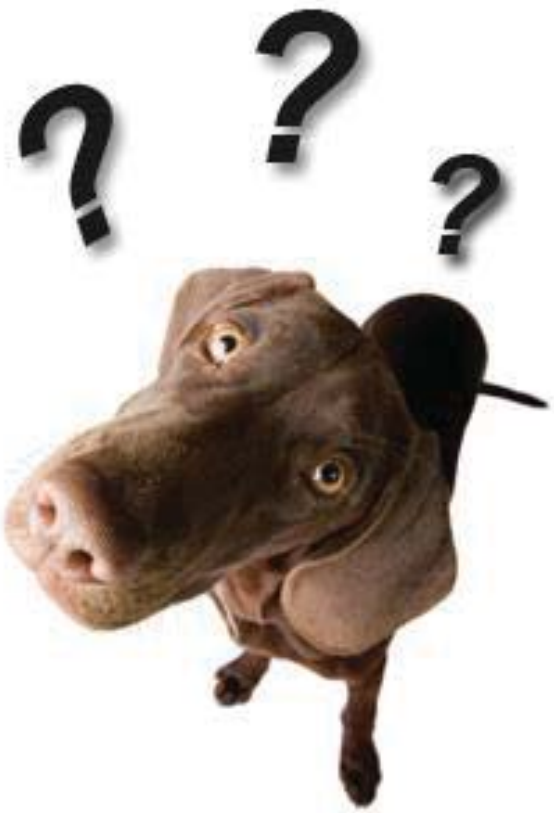
Questions



FDA Regulation of Animal Drugs

A Brief Overview of CVM's Drug Approval Process

Under the Act, the term "drug" means articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary; articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles other than food intended to affect the structure or any function of the body of man or other animals. It also includes articles intended for use as a component of a drug.

Once a product is determined to be a drug for animal use, the next step is to determine whether or not it is a new animal drug. The Act defines a new animal drug (in part) as *any drug intended for use for animals other than man, the composition of which is not generally recognized, among experts qualified by scientific training and experience, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.* By virtue of Supreme Court interpretations of the necessary basis for general recognition, there are, for all practical purposes, no animal drugs which are not also new animal drugs. The **Animal Drugs @ FDA (https://animaldrugsatfda.fda.gov/)**, accessible from the CVM Home Page contains a searchable database of all FDA-approved animal drugs.

An unapproved new animal drug may be distributed in accordance with 21 CFR Part 511 if the drug will be used for research, i.e., for the collection of data intended to be submitted in support of an NADA approval. Investigational New Animal Drug (INAD) regulations provide that such drugs may be distributed for use only by experts, qualified by scientific training and expertise, to investigate the safety and effectiveness of animal drugs.

Before a new animal drug may receive FDA approval, the sponsor must establish that the new animal drug is safe and effective.

> Safe includes safety to the animal, safety of food products derived from the animal, safety to persons administering the drug or otherwise associated with the animal, and safety in terms of the drug's impact on the environment.
>
> Effective means that the product will consistently and uniformly do what the labeling claims it will do.

Drug sponsors submit a New Animal Drug Application (NADA) along with supporting data, including all adverse effects associated with the drug's use. The NADA must also include information on the drug's chemistry; composition and component ingredients; manufacturing methods, facilities, and controls; proposed labeling; analytical methods for residue detection and analysis if applicable; an environmental assessment; and other information. The sponsor of a new animal drug is responsible for submitting all appropriate data to establish effectiveness and safety. If the drug product is intended for use in a food-producing animal, residues in food products must also be established as safe for human consumption.

FDA review of the NADA submitted by drug sponsors is very detailed and comprehensive. FDA scientists will determine whether the data have been developed in accordance with either Good Laboratory Practice Regulations or clinical trial guidance. If the studies were conducted properly, the data are evaluated with respect to drug safety and effectiveness. The animal safety data for a drug product must relate to the dosage levels and routes of administration proposed in the labeling. The primary objective is to determine the safety of the product relative to labeled usage.

At the conclusion of the animal safety review, a summary is prepared which explains why the product is safe or not shown to be safe. If the product has been shown to be safe but some restrictions or constraints on use are needed, all warning and precaution statements to be placed on the label must be enumerated and included in the summary, as well as any expected side effects.

All effectiveness data submitted must relate either directly or indirectly to the specific label and labeling claims made for the product. The sponsor must demonstrate that the product produces the claimed effect.

With respect to human food safety, it is the responsibility of the producer or sponsor of the animal drug to furnish FDA with the scientific information and experimental data that demonstrate that the presence of residues of the animal drug in the edible food products of the animal are safe for the consumer of the food product. The term "residues" applies to the parent drug and/or its metabolites. Detailed guidance on the studies required for animal drug approval is available from the Center for Veterinary Medicine (CVM). To assure that human food of animal origin can be monitored for the presence of drug residues, FDA requires sponsors of drugs for food animal use to provide acceptable analytical methods capable of determining and confirming the animal drug or its metabolites in the animal tissue.

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Classifying RX and OTC Animal Drugs

FDA is responsible for determining the marketing status (prescription, over-the-counter, or VFD) of animal drug products based on whether or not it is possible to prepare "adequate directions for use" under which a layperson can use the drugs safely and effectively. Prescription (Rx) products can be dispensed only by or upon the lawful written order of a licensed veterinarian. Safe use includes safety to the animal, safety of food products derived from the animal, safety to the persons associated with the animal, and safety in terms of the drug's impact on the environment.

Effective use of a drug product assumes that an accurate diagnosis can be made with a reasonable degree of certainty, that the drug can be properly administered, and that the course of the disease can be followed so that the success or lack of success of the product can be observed.

The same drug substances can be marketed in a number of different dosage forms, intended for use by different routes of administration, and in different species of animals. Thus, these drug products may be appropriately labeled Rx in some cases and OTC in others. Rx products must bear the legend:

"Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."

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Dispensing Veterinary Prescription Drugs

Since adequate directions for safe and effective lay use cannot be written for animal prescription drug products, such products can only be sold on the prescription or other order of a licensed veterinarian (Section 503(f)). Prior to being sold or dispensed, they must remain in the possession of a person or firm regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of animal prescription drug products. The drug products may be distributed only by persons or firms authorized by State and local laws.

Sale (dispensing, shipping, or otherwise making available for use in animals) of an animal prescription drug product to the layperson may be made only by or on the bona fide prescription or other order of a licensed veterinarian. Sale of a animal prescription drug product to a layperson, except on a prescription or on order of a licensed practitioner, causes the product to be misbranded and subjects the seller to civil and/or criminal provisions of the Act.

A licensed veterinarian may legally use or dispense an animal prescription drug product only within the course of his/her professional practice where a valid veterinarian-client-patient relationship exists. Veterinarians employed by drug manufacturers or distributors may not legally dispense prescription drug products to laypersons unless they meet the above criteria. Similarly, practicing veterinarians or their employees may not legally sell animal prescription drug products to walk-in customers unless the same criteria are met. Federal regulations require that drug manufacturers provide at least the following information on the label of the finished package form of animal prescription drug products:

What information needs to be on the package label of animal Rx drugs?

- the statement, "*Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian*;"
- recommended or usual dosage;
- route of administration, if it is not for oral use;
- quantity or proportion of each active ingredient as well as the information required by section 502(e) of the Act;
- names of inactive ingredients if it is for other than oral use;
- an identifying lot or control number from which it is possible to determine the complete manufacturing history of the drug.

What needs to be included in the veterinarian's prescription and included on the label of the dispensed product?

- name and address of the dispenser;
- serial number and date of the order or its filling;
- name and address of the veterinarian who prescribed or ordered the drug product;
- directions for use; and
- any necessary warning and precautionary statements including withdrawal times.

Any additional requirements of State or local laws for dispensed animal drug products must also be followed.

To protect themselves and their clients, veterinarians should make efforts to ensure their instructions are followed, especially when they prescribe or recommend drugs for food-producing animals that require a withdrawal period.

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Compounding of Animal Drugs

To be legally marketed, new animal drugs must be approved under section 512 of the FD&C Act, conditionally approved under section 571 of the FD&C Act, or included on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species under section 572 of the FD&C Act. The FD&C Act does not generally distinguish between compounding and other methods of animal drug manufacturing. Animal drugs that are not approved or indexed are considered "unsafe" under section 512(a)(1) of the FD&C and adulterated under section 501(a)(5) of the FD&C Act. Animal drugs compounded from bulk drug substances are new animal drugs.

On May 19, 2015, FDA revoked Compliance Policy Guide, Section 608.400, “Compounding of Drugs for Use in Animals" and published a draft guidance that provided information to compounders of animal drugs and other interested stakeholders on FDA’s enforcement approach with respect to the compounding of animal drugs from bulk drug substances. Compliance Policy Guide 608.400 was withdrawn because it was no longer consistent with FDA’s current thinking. After reviewing the comments submitted to the docket, the FDA decided not to finalize the current draft guidance, and will instead develop and issue a new draft guidance. In developing the new draft, the FDA will carefully consider the issues that are specific to compounding of animal drugs, including the significance of using compounded drugs as a treatment option in various veterinary settings and animal species. Until we publish final guidance on this issue, FDA intends to look at the totality of the circumstances when determining whether to take enforcement action for unlawful animal drug compounding activities.

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Resources for You

- From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process (/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm)

More in Resources for You (/AnimalVeterinary/ResourcesforYou/default.htm)

For Industry (/AnimalVeterinary/ResourcesforYou/ucm508946.htm)

For Veterinarians (/AnimalVeterinary/ResourcesforYou/ucm214771.htm)

Publicaciones en Español del Centro de Medicina Veterinaria (CVM) (/AnimalVeterinary/ResourcesforYou/ucm135578.htm)

Animal Health Literacy (/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/default.htm)

Unapproved Animal Drugs

For all inquiries, complaints and questions regarding potential Unapproved Animal Drugs, please e-mail: **CVMUnapprovedDrugs@fda.hhs.gov (mailto:CVMUnapprovedDrugs@fda.hhs.gov)**.

What are Unapproved Animal Drugs?

FDA considers an “unapproved animal drug” to be a drug that:

- Is intended for use in animals; and
- Meets the definition of “new animal drug” in the Federal Food, Drug, and Cosmetic (FD&C) Act; but
- Does not have legal marketing status, meaning FDA has not **approved**, **conditionally approved**, or **indexed the drug**.

To better understand this, a couple of definitions are in order.

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First, what’s a drug? The FD&C Act defines “drug” to include, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”[1]

The intended use of a product determines if it’s a drug. Here are a few examples to illustrate this concept:

- When a company sells bottled water for people to drink as a beverage, the water is not a drug. But if the company sells those same bottles of water as a cure for cancer in dogs, then the water is a drug under the FD&C Act because the intended use is to cure a disease (cancer) in dogs.
- When a company sells formaldehyde for a car manufacturer to use to make automotive parts, it’s not a drug. But when a company sells formalin—a solution of formaldehyde—for a fish biologist to use to kill external parasites

on finfish, it's a drug under the FD&C Act because the intended use is to treat a disease (parasitism) in fish.

- When a company sells a product claiming it makes cows ovulate at the same time, the product is a drug. Although it's not treating or preventing a disease in the cows, the product's intended use is to change how their bodies function, which makes it a drug under the FD&C Act.

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Second, what's a new animal drug? The FD&C Act defines "new animal drug" as a drug intended for use in animals that is not ***Generally Recognized As Safe and Effective (GRASE)*** **(http://www.accessdata.fda.gov/scripts/cder/training/OTC/topic3/topic3/da_01_03_0040.htm)** by qualified experts for the uses listed on the label.[2] Taken in the reverse, if a drug is GRASE, then it's not a new animal drug under the FD&C Act. For an animal drug to be GRASE, the experts must generally agree that, based on published studies, the drug is safe and effective for its intended uses.

There is a very narrow exception to the definition of a new animal drug and that is grandfathered drugs. For an animal drug to be grandfathered, it must have been approved under the 1906 Food and Drug Act and before June 25, 1938 (the date President Franklin Roosevelt signed the FD&C Act into law), and its label and composition have not changed since that time. If a drug is grandfathered, then it's a not a new animal drug under the FD&C Act.

FDA thinks it's very unlikely that any currently marketed animal drug would be considered GRASE or would qualify for the "grandfather" exception. And so, if a drug is intended for use in animals, it's almost certain to be a new animal drug.

The entire term "new animal drug" is defined by law and applies to any product which fits that definition. The adjective "new" doesn't mean the drug just went on the market; some "new animal drugs" have been marketed for years. For example, the drug ivermectin has existed for decades and even though FDA originally approved it to prevent heartworm disease in dogs in March 1987,[3] ivermectin is still a "new animal drug" under the FD&C Act.

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FDA Pre-Market Review & Legal Marketing Status

As required by the FD&C Act, new animal drugs must be reviewed by FDA for safety and effectiveness and obtain legal marketing status before they can be marketed. The pre-market review is integral to FDA's ability to protect animal and public health. During the review, the agency evaluates information submitted by the drug company to make sure the drug is safe and effective for its intended use and that the drug is properly manufactured and properly labeled.

The FDA pre-market review is also necessary for the drug to obtain legal marketing status through an approval, conditional approval, or indexed listing.[4] After the drug company gets a new animal drug approved, conditionally approved, or indexed by FDA, the company can legally market it for the uses listed on the label.

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Unapproved Animal Drugs

Unapproved animal drugs are new animal drugs that don't have legal marketing status. They have not been approved, conditionally approved, or indexed by FDA. It's illegal for drug companies to market unapproved new animal drugs because they haven't gone through the FDA pre-market review and obtained legal marketing status under the FD&C Act. Unapproved animal drugs may not meet the agency's strict standards for safety and effectiveness and may not be properly manufactured or properly labeled.

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Three Pathways to Legal Marketing Status

Approval

An approved animal drug has gone through the New Animal Drug Application (NADA) process, or for an approved generic animal drug, the Abbreviated New Animal Drug Application (ANADA) process. If the information in the NADA or ANADA meets the requirements for approval, FDA approves the animal drug. FDA's approval means the drug is safe and effective when it is used according to the label. FDA's approval also ensures that the drug's strength, quality, and purity are consistent from batch to batch, and that the drug's labeling is truthful and complete.

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Conditional Approval

A conditionally approved animal drug has gone through the New Animal Drug Application process except the drug has not yet met the effectiveness standard for full approval. FDA's conditional approval means that when used according to the label, the drug is safe and has a "reasonable expectation of effectiveness."

The conditional approval is valid for one year. The drug company can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. During the 5-year period, the drug company can legally sell the animal drug while collecting the remaining effectiveness data. After completing the effectiveness requirement, the company then submits an application to FDA for full approval. The agency reviews the application and, if appropriate, fully approves the drug. Conditional approval is only available for drugs for minor species or minor uses in a major species.

Minor species are all animals that are not major species. The seven major species are cattle, horses, pigs, chickens, turkeys, dogs, and cats. Ferrets, eagles, fish, and sheep are examples of minor species.

A minor use in a major species is using a drug in a major species for a condition that occurs:

- Infrequently and in only a small number of animals each year; or
- In limited geographic areas and in only a small number of animals each year.

For example, using a drug to treat a rare disease in dogs is a minor use in a major species.

Learn more about minor species and minor uses by visiting the following website:

Lions and Tigers and Bears! OMUMS! (/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm189540.htm)

Learn more about the drug approval process by visiting the following websites:

- **New Animal Drug Applications (/AnimalVeterinary/DevelopmentApprovalProcess/NewAnimalDrugApplications/default.htm)**; and
- **From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process (/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm)**

Learn more about the conditional drug approval process by visiting the following website:

- **Minor Use/Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)**

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Indexing

An indexed animal drug is a drug on **FDA's Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm125452.htm)**, referred to as "the Index." Although technically unapproved, a drug listed on the Index has legal marketing status. It can be legally marketed for a specific use in certain minor species. Indexing is allowed for drugs for:

- Non-food-producing minor species, such as pet birds, hamsters, and ornamental fish. These animals are typically not eaten by people or food-producing animals; and
- An early non-food life stage of a food-producing minor species, such as oyster spat (immature oysters). Because people do not generally eat oyster spat, a drug to treat a disease in spat can be indexed, but a drug to treat a disease in adult oysters, which people commonly eat, cannot be indexed.

Indexing a drug is a three-step process. A panel of qualified experts outside FDA reviews the drug's safety in the specific minor species. The panel also reviews the drug's effectiveness for the intended use. All members must agree that, when used according to the label, the drug's benefits outweigh the risks to the treated animal. The panel submits a report containing its recommendation to FDA. If FDA agrees with the panel, the agency adds the drug to the Index.

Learn more about indexing by visiting the following websites:

- **Minor Use/Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)**; and
- **Drug Indexing (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm070206.htm)**

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1 **Section 201(g)(1)(B) & (C) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(g)(1)(B) & (C)] (http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII.htm)**
2 **See Section 201(v) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(v)] (http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII.htm)**
3 **HEARTGARD-30, New Animal Drug Application (NADA) 138-412 ()**
4 **Conditional approval and indexing, created by the Minor Use and Minor Species Animal Health Act of 2004, are only available for certain uses. (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)**

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Regulatory Actions

- **Vetoquinol N.-A. 6/29/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm576886.htm)**
- **Ocubright Tear Stain Remover, Inc. 5/16/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm559809.htm)**
- **Merit Pet Products, LLC 5/12/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm558405.htm)**

- Montana Emu Ranch Company Inc 4/20/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm556843.htm)
- Tobin's Royal Stag, Inc. dba Tobin Farms Velvet Antler 4/19/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm554024.htm)
- Nature's Treasures 4/17/17 (/ICECI/EnforcementActions/WarningLetters/2017/ucm553688.htm)
- Northern Health Products 12/22/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm536985.htm)
- Vetix Inc. 10/12/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm525191.htm)
- Buck Mountain Herbs Botanicals, Inc. 10/7/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm526534.htm)
- VetraGenics 8/9/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm518593.htm)
- Pegasus Laboratories, Inc. 8/5/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm518460.htm)
- NuVet Labs 7/29/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm525952.htm)
- Merck Animal Health 1/28/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm484445.htm)
- Diamond Animal Health Inc. 1/27/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm483679.htm)
- Dechra Veterinary Products LLC 1/27/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm483676.htm)
- Virbac Animal Health, Inc. 1/26/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm483374.htm)
- Quality Animal Care Manufacturing 1/26/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm483404.htm)
- Neogen Corporation 1/26/16 (/ICECI/EnforcementActions/WarningLetters/2016/ucm483391.htm)
- Advantage Biosciences 12/17/15 (/ICECI/EnforcementActions/WarningLetters/2015/ucm479898.htm)
- FDA takes steps to prevent sales of unapproved kidney drugs for dogs and cats (/NewsEvents/Newsroom/PressAnnouncements/ucm454500.htm)
- Hoof Health LLC dba Hoof Effects 7/9/15 (/ICECI/EnforcementActions/WarningLetters/2015/ucm455249.htm)
- Canna Companion LLC 2/24/15 (/ICECI/EnforcementActions/WarningLetters/2015/ucm435671.htm)
- Abler Inc 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm422545.htm)
- Canna Pet LLC 2/24/15 (/ICECI/EnforcementActions/WarningLetters/2015/ucm435662.htm)
- Abler Inc 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm422545.htm)
- Ceva Animal Health Pty Ltd 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm422549.htm)
- Cox Veterinary Laboratory, Inc. 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm422544.htm)
- Douglas J Gordon 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421214.htm)
- Generic frontline plus 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm422552.htm)
- Horse Gold, Inc 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421146.htm)
- HorsePreRace 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421133.htm)
- MULTIVET USA, Inc. 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421707.htm)
- Tri-Star Equine 10/29/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421167.htm)
- Canine Care 10/23/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm421217.htm)
- Little City Dogs 10/7/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm417957.htm)
- Blanc du Blanc, Inc. 8/28/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm411955.htm)
- I'm a Little Teacup 8/28/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm411975.htm)

- Petaware 8/28/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm411963.htm)
- Amber Technology, LLC 1/30/14 (/ICECI/EnforcementActions/WarningLetters/2014/ucm384594.htm)
- Amarc Enterprises 12/11/12 (/ICECI/EnforcementActions/WarningLetters/2012/ucm340266.htm)
- Untitled Letter - ProCore Laboratories, LLC 9/25/12 (/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/ucm323276.htm)

Spotlight

- What You Need to Know: FDA-Approved vs. Unapproved Animal Drugs (/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/ucm289708.htm
- FDA Issues Warning Letters to Manufacturers of Unapproved Levothyroxine Drugs for Hypothyroidism in Dogs (/AnimalVeterinary/NewsEvents/CVMUpdates/ucm482928.htm)
- FDA releases draft guidance on animal drug compounding from bulk drug substances (/NewsEvents/Newsroom/PressAnnouncements/ucm447159.htm)

More in Unapproved Animal Drugs (/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/UnapprovedAnimalDrugs/default.htm)

AVMA
Our Passion. Our Profession.

August 14, 2015

Mr. Eric Nelson
Center for Veterinary Medicine
Division of Compliance
FDA Center for Veterinary Medicine
7519 Standish Pl
Rockville, MD 20852

RE: [Docket Nos. FDA-2015-D-1176 and FDA-2003-D-0202] Compounding Animal Drugs From Bulk Drug Substances; Draft Guidance for Industry; Availability; Withdrawal of Compliance Policy Guide; Section 608.400 Compounding of Drugs for Use in Animals

Dear Mr. Nelson:

I am writing on behalf of the American Veterinary Medical Association (AVMA), established in 1863 and the largest veterinary medical organization in the world with over 86,500 members. The AVMA's mission is to lead the profession by advocating for its members and advancing the science and practice of veterinary medicine to improve animal and human health.

The AVMA recognizes that the FDA Draft Guidance for Industry #230 sets forth the Food and Drug Administration's (FDA) policy regarding compounding animal drugs from bulk drug substances by state-licensed pharmacies, licensed veterinarians, and facilities that register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b). We understand this guidance describes the conditions under which FDA generally does not intend to take action for violations of the following sections of the FD&C Act: section 512 (21 U.S.C. 360b), section 501(a)(5) (21 U.S.C. 351(a)(5)), section 502(f)(1) (21 U.S.C. 352 (f)(1)), and, where specified, section 501(a)(2)(B) (21 U.S.C 351(a)(2)(B)), when a state-licensed pharmacy, licensed veterinarian, or an outsourcing facility compounds animal drugs from bulk drug substances.

Additionally, we recognize that this draft guidance only addresses the compounding of animal drugs from bulk drug substances, and that it does not apply to the compounding of animal drugs from approved new animal or new human drugs. The AVMA was a leader in the development of, and advocacy for, the enactment of the Animal Medicinal Drug Use Clarification Act on behalf of our members and the patients they serve. Extralabel drug use, including the compounding of preparations from FDA-approved drugs, continues to provide access to critical medications and our members continue to rely on this FDA-regulated activity in the practice of veterinary medicine within the confines of the 21 CFR 530.

The AVMA appreciates the FDA's recognition that there is a need for preparations compounded from bulk drug substances. We also share the agency's concern about the use of these preparations when approved alternatives exist that can be used as labeled or in an extralabel manner consistent

with the requirements of FDA's extralabel provisions. The AVMA continues to believe that three circumstances exist wherein compounds prepared from bulk drug substances might be necessary:

- the approved product is not commercially available, or
- the needed compounded preparation cannot be made from the approved product, or
- there is no approved product from which to compound the needed preparation.

While we are formally submitting these comments today, we will continue to assess whether the draft guidance can realistically address the needs of veterinary patients and ask that the FDA continue its dialog with us.

Overarching comments

Drug Availability

Veterinary medicine is unique in that we treat a multitude of species with an even greater number of unique diseases and conditions. Approval of new animal drugs is critical to veterinary medicine and engaging with the Agency in facilitating that process remains a high priority for our Association. However, compounding from bulk drug substances is still a necessary practice for veterinarians because there are, and always will be, a limited number of FDA-approved drug products for the many species and conditions that we treat. Intermittent drug shortages and commercial unavailability of FDA-approved drug products drive the need for compounded preparations within veterinary practice. While FDA has not identified cost as appropriate reason for compounding from bulk drug substances, the AVMA acknowledges that cost can be a reason veterinarians utilize compounded preparations because that is the only way a client can afford to treat their pet.

Our members have clearly conveyed that they need access to safe and efficacious drug products that can be practicably used in their patients. While recognizing FDA's jurisdiction is limited to issues related to safety and efficacy, not cost or commercial availability of drug products, we underscore the increasingly critical need for effective pathways for drug products to achieve legal marketing status. A robust, competitive animal health industry can benefit animal patients by way of increased numbers of legally marketed products that can be prescribed, dispensed or used in the preparation of compounds.

Existing pathways to legal marketing

- We continue to support the concept of user fees, so long as those fees go toward expedited reviews. Increased numbers of both pioneer and nonproprietary approved drug products can help to minimize the impacts of drug shortages.
- FDA's indexing process can be a valuable way to increase the number of legally marketed drug products for use in minor species or in major species with rare conditions. We recognize that indexing provides a process to obtain legal marketing status for eligible products. The indexing process should be utilized to a fuller extent, or revised accordingly, so that well-vetted drugs that have undergone expert panel scrutiny can be used legally for wildlife, aquaria, zoo, aquacultural, and laboratory animal species, and for major species with rare conditions.

Innovative pathways to legal marketing

- In 2010, the FDA published a Federal Register notice FDA-2010-N-0528 seeking comments related to identification of emerging paths toward legal status of drugs that are medically necessary and manufactured using good manufacturing processes. At the time, FDA conveyed that it is open to using both the agency's existing authority and new approaches to

make more drugs legally available to veterinarians, producers, and pet owners. We commended the FDA on its pursuit at the time and urge the FDA to implement innovative strategies to legal marketing. The AVMA stands ready to discuss possible approaches further with FDA.

Non-food minor species

In species including but not limited to zoo animals, laboratory animals, exotic pets, wildlife, aquaria animals, and non-food aquacultural animals, the use of compounded preparations is unquestionably necessary. We urge FDA to carefully consider the critical need for access to compounded preparations within these species, as FDA further refines its guidance. There are few choices of FDA-approved or indexed products available for use in these species; therefore, availability of properly compounded preparations to be maintained for office use in appropriate strengths and formulations, and the ability to mix and dilute medications are necessary to provide adequate veterinary care. Several provisions within this draft guidance should not apply to non-food minor species in their respective environments, such as limiting preparations to be maintained in office for urgent or emergent needs, patient-specific prescriptions, and detailed labeling requirements for compounded preparations maintained for office use.

Federal vs. State Jurisdiction

The licensure of veterinarians is regulated by state governmental authorities. Given this is a federal guidance, not a regulation, coupled with the existence of a wide range of state compounding rules, we would appreciate clarification on how GFI #230 will be enforced by the FDA. State rules regulating compounding in veterinary practice vary greatly. Some even provide substantial permissiveness for veterinarians to obtain preparations compounded for office use, and administer and dispense from the compounded preparations maintained in their office.

- How will the FDA evaluate whether the compounding of animal drugs is done in accordance with the conditions outlined in the guidance?
- Will the FDA rely on state boards of pharmacy and boards of veterinary medicine to enforce provisions within GFI #230, and how will the FDA reconcile discrepancies between state rules and GFI #230?

Enforcement

For many years the AVMA has advocated for, and applauded, the FDA's enforcement of illegal manufacturing activities. The AVMA asserts that large-scale manufacturing of animal drugs under the guise of compounding does not serve to benefit animal health; rather, circumvention of the drug approval process yields substances with unknown safety, efficacy, and potency, potentially allowing disease to progress. Animal drug manufacturers also contend that these compounded preparations result in a supply/demand disincentive for new FDA-approved drug products.

- As FDA is concerned about the use of animal drugs compounded from bulk drug substances, especially when approved alternatives exist that can be used as labeled or in an extralabel manner consistent with the requirements of FDA's extralabel provisions, how does this guidance change the FDA's ability to take action to address these concerns?
- Does the FDA currently have the needed resources and enforcement capabilities to fully enforce all egregious compounding activities, or are new authorities and appropriations necessary for the agency?
- Will the FDA develop and provide a user's guide on implementing the GFI #230 for state boards of pharmacy, state boards of veterinary medicine, individual veterinarians, and pharmacists to follow? We anticipate that time for a transition to the new paradigm will be

needed across stakeholder groups, especially given the wide array of state rules that exist related to veterinary compounding. Some veterinary state boards might not be prepared to inspect veterinary facilities for compliance with standards delineated within GFI #230.

- How will FDA's enforcement of compounded preparations be reconciled with the Drug Enforcement Administration's expectations that preparations containing controlled substances must only be prepared pursuant to patient-specific prescriptions?
- We also encourage FDA to coordinate with all relevant governmental agencies related to use of bulk drug substances in depopulation efforts, which might be needed during large-scale national emergencies. The AVMA stands ready to serve as a resource to FDA related to this topic.

Adverse Event Reporting System

The AVMA contends that there is a need for the continued development and strengthening of adverse event reporting systems for all adverse events, including lack of efficacy. We believe that there must be a strong, science-based, transparent and systematic surveillance system, especially considering the wide scope of species and disease conditions that veterinarians treat. The AVMA supports development of a user-friendly, easy to access form for all adverse events related to compounding. A user-friendly electronic system would be anticipated to promote both reporting by those compounding, and ease of review by FDA. For example, FDA could maintain a database of recently reported adverse events for veterinarians and pharmacists to use as a resource. Sufficient and meaningful data inputs, or adverse event reports, are imperative for a strong reporting system foundation.

- Does the FDA's current 1932a form, as a means of capturing adverse events, provide the robustness FDA needs to detect and act on trends? The AVMA contends that all adverse events associated with compound preparations should be reported, not just serious adverse events. Adverse events related to lack of efficacy should also be collected and analyzed.

Comments on Specific Provisions within Draft GFI #230

Scope of AVMA Comments

The AVMA has chosen to comment on the sections and questions that impact veterinary medicine. We will defer to the pharmacy community for feedback related to the practice of pharmacy and functioning of outsourcing facilities: pharmacist supervision (Section III.A.1. and Section III.C.2); compounding in advance of receipt of a prescription (Section III.A.2); determining and documenting that the compounded drug cannot be made from the FDA-approved drug(s) (Section III.A.5); current Good Manufacturing Practices (cGMP) (Section III.C.4); certain labeling requirements (Section III.C.10); and reporting requirements from 503B of the FD&C Act (Section III.C.8).

Definitions

We request the FDA provide clarification on the following terms:

- "Outsourcing facility"—Draft GFI #230 defines an "outsourcing facility" as a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act. Section 503B(d)(4) defines an outsourcing facility as a facility at one geographic location or address that (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of that section of the law.

  As the use of outsourcing facilities in veterinary medicine is an entirely new concept, we are still assessing how the requirements for registration as an outsourcing facility would impact

the ability to meet veterinary needs. We wish to underscore that there is a substantial need for both non-sterile and sterile compounded preparations to be maintained for office use in veterinary medicine. We appreciate that the use of outsourcing facilities in the preparation of office stock is intended to increase safety of compounded preparations, yet we caution that use of outsourcing facilities might have the unintended consequence that some preparations of critical importance to animal health may no longer be available due to economic or other business considerations.

We ask the FDA to clarify how it will reconcile the clear discrepancies between statutory language and provisions in various agency documents:

- Specifically, it is our understanding that outsourcing facilities in compliance with Section 503B are only exempt from the *human drug approval requirements* in section 505 of the FD&C Act (21 U.S.C. 355), the requirement to be labeled with adequate directions for use in section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)), and the track and trace requirements in section 582 of the FD&C Act (21 U.S.C. 360eee-1). How does this guidance impact the facility's exemption from animal drug approval requirements?
- Per the FDA's draft guidance for industry *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act,* referenced in draft GFI #230, outsourcing facilities are required to meet certain conditions to qualify. Of particular concern is the requirement that the outsourcing facilities must not compound drugs that appear on a list published by the FDA of drugs that have been withdrawn or removed from the market because the drugs or components of such drugs have been found to be unsafe or not effective *for humans.* We are aware of a number of such compounded preparations needed in veterinary medicine, including but not limited to cisapride, asparaginase, and chloramphenicol. In these cases, the FDA-approved product was withdrawn from the market due to human safety concerns, leaving us with no alternative to treat animal patients.
- An additional concern is that a facility, in order to meet the definition of an outsourcing facility, must be engaged in the compounding of sterile human drugs. The draft guidance clearly states that "you should not register a facility as an outsourcing facility if the only activities conducted at the facility are…animal drugs,…because none of the products produced at the facility would qualify for the exemptions provided in section 503B." A number of pharmacies currently exist that serve the needs of veterinarians and would need to register as an outsourcing facility per GFI #230, but they are explicitly prevented from registering per Section 503B because they do not meet certain requirements and were told not to register by the agency in another Guidance for Industry.

- "Compounding" as defined within 503A does not include mixing, reconstituting, or other such acts that are performed in accordance with directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling. Defined within 503B, compounding is the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering a drug or bulk drug substance to create a drug. Is the administration of a bulk drug substance directly to an animal (for example, dissolution of metronidazole powder in aquaria for medical treatment of pet fish) considered compounding, or would administration be considered compounding only if the bulk drug

substance is mixed with another active or inactive ingredient? We ask the FDA to fully clarify its definition of animal drug compounding within this guidance.

- "Bulk drug substance" is defined within 21 CFR 207.3(a)(4) as "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances." We understand that compressed gases, household items, herbals and homeopathics, and manufactured unapproved drugs such as glucosamine, would be outside the scope of this guidance. We ask the FDA to fully clarify what it considers a bulk drug substance for purposes of this guidance.
    - In its Table 1—Estimated Annual Recordkeeping Burden, please clarify details surrounding FDA's estimate that 75,000 pharmacies will receive approximately 6,350,000 prescriptions for compounded animal drugs annually. From where were these numbers obtained, and are these numbers specific to preparations compounded from bulk drug substances or prescriptions for all compounded preparations?

- "Patient" is defined by the AVMA (https://www.avma.org/KB/Policies/Pages/Model-Veterinary-Practice-Act.aspx) as an animal or group of animals examined or treated by a veterinarian, which would include herds, flocks, groups of shelter animals, laboratory animal colonies or groups, and zoo animal and aquaria collections. We respectfully request the use of this definition for the term "patient."

- "Non-ornamental fish" needs further clarification. Which definition is the FDA using for this term? The FDA-CVM's Program Policy and Procedures Manual *Enforcement Priorities ForDrug Use In Non-Food Fish* includes a definition of "ornamental fish." For purposes of GFI #230, are all fish not included in that definition to be considered "non-ornamental fish" and therefore food-producing animals?

- "Clinical difference" is not expressly defined within Section 503B or in the draft GFI #230. How will "clinical difference" be evaluated by the FDA, or does the FDA intend to seek state enforcement of this component?

- The terms "sale" and "transferred" need to be more clearly defined. For example, does this include the sharing of a compounded preparation between one clinic and a co-owned satellite clinic, between multiple zoological institutions or government agencies, or from one university laboratory to another within the same university system?

Section III.A.

(2) We have serious concerns with the verbiage "The drug is dispensed…for an individually identified animal patient..." AVMA fully supports the requirement that a veterinarian-client-patient relationship must exist for the use of a compounded preparation in an animal patient. However, the requirement that a patient must be 'individually identified' would eliminate the ability for veterinarians to obtain a preparation for a collection of animals, such as in a zoo, laboratory animal research facility or aquarium. In some of these situations, the patient cannot be individually identified or the entire group needs to be treated; it would not be feasible or reasonable to write an individual prescription for each animal.

- We request the FDA delete the words "individually identified" and use the AVMA's definition of "patient": https://www.avma.org/KB/Policies/Pages/Model-Veterinary-Practice-Act.aspx.

(3) "Food-producing animal" defined to include all cattle, swine, chickens, turkeys, sheep, and goats is consistent with our understanding and definition of a "food-producing animal."

The AVMA contends that compounding from bulk drug substances in food-producing animals is medically necessary for certain poison antidotes, euthanasia, and depopulation medications. There must be some allowance for compounding from bulk ingredients for these explicit situations, when there is no FDA-approved product or the approved product cannot feasibly be used per label or in an extralabel fashion. Veterinarians must also be able to legally maintain sufficient quantities of these compounded preparations in their office for urgent administration needs or emergency situations in food animals. Without access, animals would die before the medication could be delivered; for example, methylene blue is needed to treat nitrate toxicosis in cattle in the southeastern part of the USA. We recognize veterinarians' need to ensure food safety, maintain required records, and label drugs appropriately, as required under FDA's extralabel drug use rules. We ask that FDA draft a separate guidance to address these needs.

We are not opposed to the requirement that the prescription or documentation accompanying the prescription for a non-food animal must contain the statement "This patient is not a food-producing animal." The statement also helps to distinguish those patients that could be a food-producing animal in some situations, independent of species (e.g., rabbits, captive elk, captive deer).

We also would appreciate clarification on the wording in the latter half of this provision: "...any other animal designated on the prescription or in documentation accompanying the prescription by the veterinarian as a food-producing animal, regardless of species, is considered to be a food-producing animal."

- Would this mean that a veterinarian would state "This patient is a food-producing animal" to identify for the pharmacist that a bulk drug substance is not to be used?

(4)(a) The AVMA disagrees with the requirement that a pharmacy may compound a preparation using a bulk drug substance that is a component of any marketed FDA-approved animal or human drug only if the change between the compounded drug and the FDA-approved drug would produce a clinical difference. We assert that compounding should be allowable if the approved product is not commercially available for other reasons (i.e., unavailable) and no therapeutic alternatives exist, or if the needed compounded preparation cannot be made from the approved product (such as preparation of metronidazole benzoate for use in a cat) as allowed per Section III.A.5. We ask the agency to amend the provision accordingly. Given the frequency of FDA-approved drug product shortages and backorders, including all marketed FDA-approved drugs is too restrictive for the needs of veterinary patients.

(4)(b) The AVMA has concerns with, and is opposed to, the requirement for a statement from the veterinarian that the compounded preparation "produces a clinical difference for the individually identified animal patient" with an explanation of that difference. We contend that a medical rationale is necessary for use of compounds, and is a more applicable term than "clinical difference." However, we believe documentation of why the compounded preparation was chosen is more appropriate for the medical record.

- Should FDA still choose to require inclusion of a statement in documentation, will the statements be evaluated by the FDA, or does the FDA intend to seek state enforcement of this component?

Additionally, we believe that the term "clinical difference" does not capture other medical needs for compounded preparations, such as certain worker and client safety needs, client compliance, and animal stress situations (e.g., fractious cats). These safety/animal handling needs are not related to clinical differences but rather, the ability to adequately medicate patients.

(5) Related to pharmacists documenting that a compounded preparation cannot be made from an FDA-approved drug, what does the FDA consider to be "acceptable documentation," and to whom will the documentation be provided?

(6)(b) In concept, the AVMA does not oppose the requirement that the statement "There are no FDA-approved animal or human drugs that can be used as labeled or in an extralabel manner under section 512(a)(4) or (5) and 21 CFR part 530 to appropriately treat the disease, symptom, or condition for which this drug is being prescribed" be documented on the prescription or documentation accompanying the prescription, because we believe veterinarians need to carefully consider their therapeutic options. However, the statement could inadvertently discourage use of FDA-approved drugs in preparing compounded medications. For example, we understand that sometimes the best starting ingredient for a pharmacist's preparation of a compounded medication is the FDA-approved drug. If the veterinarian includes the above statement, that essentially would direct the pharmacist to utilize a bulk drug substance. Moreover, the veterinarian writing the prescription would not necessarily know whether the FDA-approved drug or the bulk drug substance is best for the preparation. We wholeheartedly agree with the need for veterinarians to utilize FDA-approved products whenever feasible. We ask that FDA discuss this topic further with the AVMA.

(9) We would like clarification on the statement that "a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care." It is our understanding that under the guidance, the compounded preparation may only be dispensed by the pharmacy to the patient's owner or caretaker, a concept with which the AVMA disagrees. Does this provision in some way allow for the veterinarian to receive the compounded preparation from the pharmacy, and then administer and dispense the preparation to the patient's owner or caretaker? The AVMA asserts that the prescribing veterinarian should be able to dispense these preparations to help ensure that the medications are being used and administered appropriately by the client. Such dispensing also keeps the prescribing veterinarian more closely attuned to the current status of the patient should client questions or concerns (such as adverse events) arise.

We request that the FDA amend the provision to allow dispensing: "...a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care, or the dispensing of a compounded drug by the veterinarian to the owner or caretaker of an animal under his or her care."

Section III.B.

(1) Again, the AVMA contends that compounding should be done within the confines of a veterinarian-client-patient relationship. However, veterinarians must be able to legally maintain sufficient quantities of compounded preparations in their office for urgent administration needs or emergency situations, including compounds prepared by veterinarians and pharmacies. In fact, the

maintenance of preparations for office use is lawful for veterinarians under some states' rules. We request that the FDA include an allowance for the preparation of compounds by veterinarians in advance of a specific patient's need.

(2) For food animals, the AVMA, again, asserts that a publically available list of bulk drug substances for veterinarians to prepare poison antidotes, euthanasia, and depopulation preparations should be made available.

As previously stated in Section III (A) 3, veterinarians must also be able to legally maintain sufficient quantities of these compounded preparations in their office for urgent administration needs or emergency situations in food animals. Without access, animals would die before the medication could be delivered; for example, methylene blue is needed to treat nitrate toxicosis in cattle in the southeastern part of the USA. We recognize veterinarians' need to ensure food safety, maintain required records, and label drugs appropriately, as required under FDA's extralabel drug use rules. We ask that FDA draft a separate guidance to address these needs.

(3) If the veterinarian is prescribing a medication to be compounded in lieu of an FDA-approved drug, then there is a clinical need that has already been determined by the prescribing veterinarian. Thus the AVMA agrees with the purpose of the provision. We do not support any additional reporting or recordkeeping requirements related to this provision.

We request that the FDA amend the provision to allow for compounding from bulk ingredients if the approved product is not commercially available (either due to a backorder, shortage, or no longer marketed) or if the needed compounded preparation cannot be made from the approved product. As stated with respect to Sec. III.A.4.a., the frequency of FDA-approved drug product shortages and backorders makes inclusion of all marketed FDA-approved drugs too restrictive for the needs of veterinary patients.

(4) The AVMA supports the intentions of this provision as the AVMA believes that an FDA-approved drug product should always be used first and foremost.

(5) The AVMA supports the requirement that veterinarians compounding from bulk drug substances do so in accordance with USP—NF Chapters <795> and <797> (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).

(6) The AVMA agrees with the requirements for use of bulk drug substances that are accompanied by a valid certificate of analysis and that come from FDA-registered manufacturers.

(7) The AVMA agrees with the provision's allowance for veterinarians to administer the preparation to the patient or dispense to the owner or caretaker. The AVMA also agrees that this should all be done within the confines of a veterinarian-client-patient relationship.

The AVMA contends that dispensing practices by veterinarians should be regulated by individual state boards of veterinary medicine. We would like the FDA to clarify what the agency would consider to be the "transfer" of compounded preparations to another veterinarian or a satellite facility.

Section III.C.
(1) Please see our comments in the section below related to Appendix A. We have reservations about the outline drafted for the creation of such a list and whether patient needs can be met through the use of such a list.

(3) We do not oppose the requirement for a statement on the prescription or supporting documentation that "This drug will not be dispensed for or administered to food-producing animals." Including such a statement is important to help minimize the risk of the medication being used in a food animal.

As stated previously, the AVMA contends that compounding from bulk drug substances in food-producing animals is medically necessary for certain poison antidotes, euthanasia, and depopulation medications. There must be some allowance for compounding from bulk ingredients for these explicit situations, when there is no FDA-approved product or the approved product cannot feasibly be used per label or in an extralabel fashion. Veterinarians must also be able to legally maintain sufficient quantities of these compounded preparations in their office for urgent administration needs or emergency situations in food animals. Without access, animals would die before the medication could be delivered; one example also stated previously is methylene blue, which is needed to treat nitrate toxicosis in cattle in the southeastern part of the USA. We recognize veterinarians' needs to ensure food safety, maintain required records, and label drugs appropriately, as required under FDA's extralabel drug use rules. We ask that FDA draft a separate guidance to address these needs.

(6) As the draft guidance is currently written, outsourcing facilities would be the only way by which a veterinarian could obtain office stock of certain compounded preparations. Many of these preparations are not only needed for immediate in-house administration by the veterinarian but also for dispensing to the patient's owner or caretaker for treatment at home, up to a 14-day timeframe. This allows for dispensing for emerging needs, and to help ensure the drug is going to be effective in a particular patient. It would also help to avoid a client needing two prescriptions for one drug in a short timeframe (which could decrease compliance), and would allow time to detect any immediate adverse events (e.g., intolerance to the drug, such as seen when amlodipine results in inappetence in cats).

We request that the FDA amend the provision to allow dispensing: "...a sale or transfer does not include administration of a compounded drug by a veterinarian to a patient under his or her care, or the dispensing of a compounded drug by the veterinarian to the owner or caretaker of an animal under his or her care." This would bring the provision in line with what is allowed for physicians under Sec. 503B of the FD&C Act.

(9) At this time, the AVMA has reservations related to the requirement that a veterinarian's order state that the product will be used in a manner and in a species that complies with the list of permitted bulk ingredient uses under Appendix A. If any such list is created, it needs to be maintained properly and reflect veterinarians' needs. These concerns will be further addressed in the feedback below on Appendix A.

(10) The AVMA contends that certain information should be incorporated into labels/packaging and generally agrees with inclusion of:

a. Active ingredient(s)
b. Dosage form, strength, and flavoring, if any
c. Directions for use, as provided by the veterinarian prescribing or ordering the drug

d. Quantity or volume, whichever is appropriate
e. The statement "Not for resale."
f. The statement "For use only in [fill in species and any associated condition or limitation listed in Appendix A]."
g. The statement "Compounded by [name of outsourcing facility]."
h. Lot or batch number of drug
i. Special storage and handling instructions
j. Date the drug was compounded, and date of dispensing, if dispensed
k. Beyond use date (BUD) of the drug
l. Name of veterinarian prescribing or ordering the drug
m. The address and phone number of the outsourcing facility that compounded the drug
n. Inactive ingredients
o. The statement "Adverse events associated with this compounded drug should be reported to FDA on a Form FDA 1932a."
p. If the drug is compounded pursuant to a patient specific prescription, the species of the animal patient, name of the animal patient, number of refills if applicable, and name of the owner or caretaker of the animal patient. We wish to underscore that "patient" can also mean a herd, collection or group of shelter animals. We assert that the AVMA's definition of "patient" should be used.

We also request that FDA require all compounded preparations be labeled that they are not FDA-approved products. We believe it is important for consumers to recognize that safety, efficacy, potency and sterility, where applicable, of compounded preparations have not been assessed or verified by the FDA.

Labeling requirements for preparations to be maintained for office use can be difficult for minor species, including but not limited to zoo, aquaria, laboratory-animal, and wildlife collections and/or facilities. For example, some compounds maintained for office use will be used to treat lameness in a number of species in a zoo collection. The labeling requirement as posed in (f) would be particularly difficult in these collections.

Pertaining to Provisions Which Appear in Multiple Sections
Related to Labeling by Pharmacies and Veterinarians (Section III.A.11 and Section III.B.9)
AVMA requests that the labeling requirements for pharmacists and veterinarians include name of client; veterinarian's name and address; identification of animal(s) treated, species and numbers of animals treated, when possible; date of dispensing; name, active ingredient, and quantity of the drug preparation to be dispensed; drug strength (if more than one strength available); dosage and duration; route of administration; number of refills; cautionary statements as needed; beyond use date; and the statement "Compounded by [name, address, and contact number of the pharmacy or veterinarian]." We also assert that compounded preparations should be labeled that they have not been approved by FDA. Patient owners or caretakers should have information available to contact the compounding entity, be it a pharmacy, veterinarian or outsourcing facility.

The AVMA agrees with inclusion of the name of the owner or caretaker and species of animal. AVMA contends that a patient may be an animal or group of animals so the "name" of the animal patient should only be required for prescriptions where applicable and appropriate.

Related to Patient-Specific Prescriptions (Section III.A.2 and Section III.B.1)
Veterinarians must be able to legally maintain sufficient quantities of compounded preparations in their office for urgent administration needs or emergency situations. These cannot be obtained through patient-specific prescriptions. Examples are many, and include: methylene blue to treat nitrate toxicosis; apomorphine to induce emesis in dogs; antibiotics, such as metronidazole, formulated into an appropriate dose for small dogs and cats and a palatable flavor for non-human primates to treat acute diarrhea; and nonsteroidal anti-inflammatory drugs, such as meloxicam, for pain control in small mammals.

This guidance's allowance that preparations that appear in a list will only be available from an outsourcing facility will greatly restrict veterinarians' access to critical medications and hamstring their ability to provide appropriate care in a timely manner. We must ask the FDA to reconsider provisions related to preparations compounded for office use and engage in discussion with the AVMA and the veterinary profession to better ascertain how to best meet the needs of both the FDA and veterinary patients.

Related to Sourcing of, and Information on, Bulk Drug Substances (Section III.A.7, Section III.B.6, and Section III.C.5)
Section III.A.7 states that "Any bulk drug substance used to compound the drug is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 510) and is accompanied by a valid certificate of analysis." How does the intent related to this statement differ from the intents for Section III.B.6 and Section III.C.5, which both state "Any bulk drug substance used is manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis"?

The AVMA agrees with the requirement that any bulk drug substance used by either a pharmacy, veterinarian, or outsourcing facility be manufactured by an establishment that is registered under section 510 of the FD&C Act (21 U.S.C. 360) (including a foreign establishment that is registered under section 360(i)) and is accompanied by a valid certificate of analysis.

Related to USP-Related Requirements (Section III.A.8 and Section III.B.5)
The AVMA asserts that compliance with USP guidelines continues to be an element that can be utilized when a veterinarian considers the quality of a compounding pharmacy's preparations. The AVMA supports the requirement that veterinarians, outsourcing facilities, and pharmacists compounding from bulk drug substances do so in accordance with USP—NF Chapters <795> and <797> (e.g., a sterile drug is compounded in an area with air quality that meets or exceeds ISO Class 5 standards (see USP—NF Chapter <797>, Table 1)).

Related to the Sale or Transfer of Compounded Preparations (Section III.A.9 and Section III.B.7)
The AVMA advocates that compounded preparations should not be wholesaled. However, we seek clarification from FDA related to the definition of "sale" and "transfer" as indicated previously in our comments.

Related to Adverse Event Reporting Requirements (Section III.A.10, Section III.B.8, and Section III.C.7)
The AVMA advocates for robust, strong adverse event reporting systems. However, we ask whether the FDA's current 1932a form, as a means of capturing adverse events, provides the robustness FDA

needs to detect and act on trends? The AVMA underscores that all adverse events associated with compounded preparations should be reported by those compounding the preparations, rather than just serious adverse events. Adverse events related to lack of efficacy should also be collected and analyzed.

The AVMA contends there is a need for the continued development and strengthening of adverse event reporting systems for all adverse events, including lack of efficacy. We believe there must be a strong, science-based, transparent and systematic surveillance system, especially considering the wide scope of species and disease conditions that veterinarians treat. The AVMA supports development of a user-friendly, easy to access form for all adverse events related to compounding. A user-friendly electronic system would be anticipated to promote both reporting by those compounding and ease of review by the FDA. For example, the FDA could maintain a database of recently reported adverse events for veterinarians and pharmacists to use as a resource. Sufficient and meaningful data inputs, or adverse event reports, are imperative for a strong reporting system.

Related to the proposed requirement for submission of all adverse events within 15 days, the AVMA asserts that this timeframe is acceptable for veterinarians. We hope that such a timeframe is amenable to pharmacies and outsourcing facilities.

Appendix A, List of Bulk Drug Substances That May Be Used By An Outsourcing Facility to Compound Drugs for Use in Animals

In GFI #230, the FDA conveys its general intent to enforce all adulteration and misbranding provisions of the FD&C Act against entities compounding animal drugs from bulk drug substances if they are not in accordance with provisions delineated within the guidance. The AVMA understands this to mean that while all compounding from bulk drug substances continues to be illegal, those activities not provided for within the confines of GFI #230 are subject to *greater* likelihood of enforcement.

Although we want compounded preparations that veterinarians maintain for office use to be safe, we have concerns that the explicit use of outsourcing facilities might have the unintended consequence of making some preparations unavailable.

The AVMA asserts that use of a compounded preparation should be limited to those individual patients for which no other method or route of drug delivery is practical; those drugs for which safety, efficacy, and stability have been demonstrated in the specific compounded form in the target species; or disease conditions for which a quantifiable response to therapy or drug concentration can be monitored. Needs vary greatly across species treated by veterinarians.

- Zoo animals, laboratory animals, wildlife, exotic pets, camelids, aquaria species, and non-food aquacultural species: These minor species have few FDA-approved animal or human drug products or indexed drugs that can be used as labeled or in an extralabel manner to treat conditions. For example, diminutive dosages and volumes are required for some exotic pets, so office use is critical. Zoo veterinarians have advised they need to have office stock to be able to readily treat lameness or other conditions that can arise at any time among the large collections of animals they treat. For that reason, the importance of having preparations compounded from bulk drug substances in anticipation of the patient's need and available in the hospital or clinic for administration, and dispensing when appropriate, is undeniable.
- Food-producing animals: The AVMA suggests that the FDA draft a separate guidance to address compounding from bulk drug substances for food producing animals. The draft GFI

#230 provides no allowance for the preparation of compounds from bulk drug substances for food-producing animals. The AVMA has advocated for a publically available, current list of bulk drug substances that can be legally compounded within a veterinarian-client-patient relationship specific and limited to euthanasia, depopulation, and poison antidote compounds for food-producing animals. There currently exist no FDA-approved animal or human drug products or indexed drugs that can be used for these specific needs. Therefore, it is imperative that veterinarians have these preparations available and in their clinic when the need arises. Not only is compounding from bulk drug substances necessary for food-producing animals, the FDA must allow for the preparations to be obtained in anticipation of a specific patient's need (i.e. via a nonpatient-specific prescription or prescription order) for treating certain toxicoses and for euthanasia or depopulation.

- Dogs, cats, and horses: While there are a number of FDA-approved drug products for dogs, cats and horses, there remain circumstances where there is no FDA-approved drug product available to treat a particular animal with a particular condition, because either no drug product is approved for a specific animal species or no approved drug product is available or feasible for use under the extralabel drug use provisions. For example, some shelters receive 20,000 to 30,000 animals per year and have immediate needs that require compounded preparations for adequate treatment. Another example is the need for compounded buprenorphine when an owner is unable to adequately medicate their painful cat with the injectable or oral treatment at home. In instances such as these, having access to these compounded preparations for administration and dispensing by the veterinarian is critical to preventing animal suffering and death.

The criteria that all substances must meet to be included on the list are challenging.

- As asked previously, will the identified "significant safety concern specific to the use of the bulk drug substance to compound animal drugs" be related to safety concerns for humans or for animal patients? For example, cisapride was removed from the market due to human safety concerns, but is critical in feline medicine. We contend that safety concerns related to the use of compounded medications in human medicine should have no bearing on their use in animal patients in most circumstances.
- Additionally, evidence clearly indicating the ineffectiveness of a substance to be used should be a criterion by which the substance is not included on the list.

We have concerns related to the feasibility of creating an all-encompassing list of bulk drug substances within the paradigm framed by FDA, with supporting documentation as outlined in the Docket No. FDA-2015-N-1196. In lieu of the list, we contend that compounding from bulk drug substances should be allowed in three general sets of circumstances: the approved product is not commercially available, the needed compounded preparation cannot be made from the approved product, or there is no approved product from which to compound the needed preparation.

AVMA will be providing a separate set of comments pursuant to the Federal Register notice titled, "List of Bulk Drug Substances That May be Used by an Outsourcing Facility to Compound Drugs for Use in Animals."

Specific Topics for Comment

Should the final guidance address the issue of FDA-approved animal and human drugs that are in shortage or are otherwise unavailable (e.g., disruptions in the manufacture or supply chain; business

decisions to stop marketing the drug; drug is subject to Agency action based on safety, effectiveness, or manufacturing concerns)?
The AVMA is committed to the continued availability of medicinal products that are pure, safe, potent and efficacious for animals. While we recognize that many factors can impact a manufacturer's decision or ability to produce and make FDA-approved drug products available, the short and long-term breaks in availability or complete withdrawal of a product from the market make access to compounded preparations even more important. Lack of information regarding why the products have been removed from the market and when they might return causes frustration and uncertainty for veterinarians and pet owners as they plan for treatment of patients.

Accordingly, the AVMA contends that the lack of commercially available FDA-approved drug products is a valid reason for veterinarians to prescribe compounds prepared from bulk drug substances for patients. For example, ticarcillin-clavulanic acid is critical for treatment of certain types of bacterial otitis externa in dogs and must be compounded when commercially unavailable. We ask that the final guidance address the issue of compounding preparations from bulk drug substances when the FDA-approved drug products are unavailable for any reason. As requested earlier in our comments, does the FDA have the needed resources to address and minimize impacts of drug unavailability on patient care? Additionally, what protocols and procedures will FDA follow to assure that timely notification is made regarding emerging drug shortages that impact veterinary medicine and notification when the drug is once again commercially available? And how does FDA know when a shortage of a human FDA-approved drug will impact veterinary medicine?

How should these situations be addressed in the final guidance?
The AVMA contends that a robust, nimble, current drug shortage list should be made publically available. While we do not yet have a recommendation on whether this action should be incorporated into the provisions delineated within GFI #230, implemented elsewhere for the agency to manage, or maintained by an external stakeholder(s), appropriate resources must be dedicated toward its continual upkeep. In the interim, any role that the FDA plays with regard to identification of drug shortages needs to be well-informed and more broadly encompassing than the current list housed at
http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm267669.htm.

How should the final guidance define the terms "shortage" and "unavailable"?
A "shortage" refers to insufficient quantities of a needed FDA-approved product. "Unavailable" means that the FDA-approved product is entirely inaccessible to practitioners. Shortages and unavailability of products may be due to a back order, temporary discontinuation, or other supply interruption, resulting in limited or no accessibility through regular distribution channels.

What criteria should FDA use to determine if an approved animal or human drug is in shortage or otherwise unavailable?
FDA should consider products that are backordered, temporarily discontinued, no longer marketed, or provided intermittently in limited quantities when determining whether a product is in shortage or unavailable.

Do United States Pharmacopeia and National Formulary (USP-NF) [2] chapters <795> and <797> provide suitable standards for animal drugs compounded by veterinarians, and if not, what standards of safety, purity, and quality should apply to animal drugs compounded by veterinarians?
The USP chapters 795 and 797 are suitable standards for compounding from bulk drug substances by veterinarians.

Should licensed veterinarians be able to sell or transfer an animal drug compounded from bulk drug substances by a State-licensed pharmacy or an outsourcing facility to owners or caretakers of animals under the veterinarian's care?
We seek FDA's clarification related to the definitions of "sell," "transfer," and "dispense" before we can provide feedback related to this concept. In general, we assert that the prescribing veterinarian should be able to dispense preparations compounded by pharmacies or outsourcing facilities to his or her clients.

How should FDA apply the condition to identify an individual patient when it is not possible to identify an individual animal (e.g., koi in a koi pond)?
The AVMA contends that a "patient" is an animal or group of animals examined or treated by a veterinarian and does not need to always be individually identified. So long as the licensed veterinarian is meeting the requirements of his/her state veterinary practice act with respect to prescribing, then being able to identify an individual patient when it is not possible is unnecessary.

Should facilities registered as outsourcing facilities under section 503B of the FD&C Act be able to compound animal drugs from bulk drug substances that do not appear on Appendix A for an individually identified animal patient under conditions similar to those applicable to state-licensed pharmacies (i.e., the conditions contained in section III.A. of the draft guidance)?
Yes, so long as the outsourcing facility is a state-licensed pharmacy.

Is additional guidance needed to address the repackaging of drugs for animal use?
- *How widespread is the practice of repackaging drugs for animal use?*
- *What types of drugs are repackaged for animal use, and why are they repackaged?*
- *Have problems been identified with repackaged drugs for animal use?*

We understand repackaging to mean "The act of taking a finished drug product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the drug. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients." If this is FDA's definition, the AVMA agrees and understands that veterinarians sometimes need to repackage drugs, including compounded preparations, into smaller aliquots for administration by the owner or agent, as long as the repackaging does not affect the stability, efficacy, purity, safety, and potency of the product (e.g., light-sensitive drugs).

Is additional guidance needed to address the compounding of animal drugs from approved animal or human drugs under section 512(a)(4) or (a)(5) of the FD&C Act and part 530?
No. The AVMA was a key leader in the development and advocacy for the Animal Medicinal Drug Use Clarification Act on behalf of our members and the patients they serve. Extralabel drug use, including the preparation of compounds from FDA-approved drugs, continues to be a needed activity in veterinary medicine, and our members continue to utilize this FDA-regulated activity in the practice of veterinary medicine, within the confines of the 21 CFR 530.

Is additional guidance needed to address the compounding of animal drugs from bulk drug substances for food-producing animals?
Yes. The AVMA suggests that the FDA draft a separate guidance to address compounding from bulk drug substance for food producing animals.

The AVMA continues to recommend that there be a publically available, current list of bulk drug substances that can be legally compounded within a veterinarian-client-patient relationship specific and limited to euthanasia, depopulation, and poison antidote compounds for food animal species. If adequate scientific information is not available to determine a withdrawal time, the AVMA contends that the compounded preparation cannot be used in a food animal or the treated animal cannot enter the food supply.

As one condition under which FDA does not generally intend to take action for certain violations of the FD&C Act if this and the other conditions are followed, FDA is proposing that State-licensed pharmacies and veterinarians report any product defect or serious adverse event associated with animal drugs they compound from bulk drug substances to FDA within 15 days of becoming aware of the product defect or serious adverse event. Outsourcing facilities are required to report adverse events associated with the drugs they compound. FDA believes it is important to receive this information from State-licensed pharmacies and veterinarians because there are no other State Departments of Health or Federal Agencies (e.g., the CDC) charged with identifying and tracing animal injuries or disease associated with an animal drug compounded by these entities. FDA has the following specific questions with respect to this proposed condition:

- *How many State-licensed pharmacies and veterinarians compound animal drugs from bulk drug substances and would potentially be reporting product defects and serious adverse events to FDA?*
  We are unaware of any data that could assist in answering this question. Anecdotally, we understand that few veterinarians personally compound from bulk drug substances.

- *Are State-licensed pharmacies and veterinarians reporting the same or similar information to any State regulatory agency (e.g., State boards of pharmacy, State boards of veterinary medicine)? If so, how many reports on average does each State-licensed pharmacy and veterinarian submit to these State agencies each year?*
  It is our understanding that adverse events are grossly underreported to FDA; however, members have conveyed that when they do report an adverse event, they generally report the adverse event to the respective compounding pharmacy. We do not know the actual number of these reports, nor are we aware of the number of events reported by veterinarians to their state boards.

- *For purposes of the guidance, how should FDA define the terms "product defect" and "serious adverse event"?*
  AVMA contends that "serious adverse events" are ones that are fatal, life-threatening, require professional intervention, cause an abortion, stillbirth, infertility, congenital anomaly, prolonged or permanent disability, or disfigurement as referenced in 21 CFR 514.3.

  A "product defect" would include any obvious physical abnormalities, such as consistency, color and precipitant materials or contents, or problems with the amount, type or effectiveness of an ingredient triggered by production errors, poor quality bulk drug substances, or problems with transportation and/or storage. Any obvious physical defects of the container, seal or stopper and of the label of the product container would also constitute a product defect.

AVMA believes lack of efficacy is an adverse event and should be included in any reporting system.

- *Can FDA achieve the same objective of identifying and tracing the source of injuries or disease associated with an animal drug compounded from a bulk drug substance through means other than product defect and serious adverse event reporting, and if so, what other means? For example, would reports of product defects alone achieve the same objective?* We are unable to provide a clear answer without additional definitions for the terms "product defect" and "serious adverse event," which would help inform our understanding and opinion.

We appreciate the opportunity to comment on the draft Guidance for Industry and provide needed feedback on behalf of the AVMA's membership. For questions or concerns regarding the AVMA's comments, please contact Drs. Ashley Morgan (amorgan@avma.org; 202-289-3210) and Lynne White-Shim (lwhite@avma.org; (800) 248-2862 ext. 6784).

Sincerely,

W. Ron DeHaven, DVM, MBA
CEO and Executive Vice President

October ##, 2015

Commissioner Stephen Ostroff, M.D.
Food & Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Dear Commissioner Ostroff:

We are writing to express our serious concern with FDA's proposed "Guidance for Industry - Compounding Animal Drugs from Bulk Drug Substances", which the agency issued on May 19, 2015. Through a draft guidance, FDA is proposing a new regulatory scheme for compounded animal drugs that prohibits veterinarians from properly treating their animal patients. These fundamental changes are proposed despite the fact that Congress has not passed any statute giving FDA the broad authority it would need to make such a substantial change in animal health.

Under the proposed guidance, veterinarians would be singled out as the only health care professionals required to document in writing a clinical need before they can prescribe a medication. The draft guidance mandates very specific language that veterinarians must include on each and every prescription for a compounded preparation. This represents an unprecedented and dangerous intrusion into the state-regulated practice of veterinary medicine

The draft guidance also eliminates the ability of veterinarians to maintain an office stock of medications from compounding pharmacies that are necessary for animal health. This access to important compounded medications, commonly referred to as "office use," is permitted under most state laws. Office use of compounded medications is critical in the practice of animal health because veterinary clinics often serve as emergency rooms and hospitals for animals, and certain compounded medications must be immediately available in order to insure proper patient outcomes.

Through the draft guidance, the agency establishes and authorizes §503B outsourcing facilities to compound and distribute medications for veterinary use. When Congress established that category of FDA-registered and regulated facilities within the Drug Quality and Security Act of 2013, it was specific to the provision of sterile drug products for human use. The agency has far exceeded its authority by presuming to extend these entities into veterinary medicine.

This proposed guidance takes portions of the statute related to compounding contained in the Drug Quality and Security Act and attempts, without authorization and through a guidance document, to apply these provisions to animal drug compounding despite the fact that the Act is expressly limited to human compounding. If FDA believes that fundamental changes are needed in the regulation of animal drug compounding, the agency should instead submit a specific legislative proposal for Congress to consider. As a result, we ask that you withdraw this proposed guidance.

Thank you for your attention in this matter. We look forward to the withdrawal of this proposed guidance and please do not hesitate to contact our offices if you require any further information.

Sincerely,

Matt Salmon
Member of Congress

Kurt Schrader
Member of Congress

Contact Greg Soften (greg.safsten@mail.house.gov) in Rep. Salmon's office, or Chris Huckleberry (huck@mail.house.gov) in Rep. Schrader's with questions and to sign onto the letter.

KeyCite Red Flag - Severe Negative Treatment
Order Vacated, Appeal Dismissed by U.S. v. Franck's Lab, Inc., 11th Cir.(Fla.), October 18, 2012

816 F.Supp.2d 1209
United States District Court,
M.D. Florida,
Ocala Division.

UNITED STATES of America, Plaintiff,
v.
FRANCK'S LAB, INC., et al., Defendants.

Case No. 5:10–cv–147–Oc–32TBS.
|
Sept. 12, 2011.

Synopsis

Background: Food and Drug Administration (FDA) brought action seeking to enjoin state-licensed pharmacy from engaging in bulk compounding of animal drugs. Following denial of pharmacy motion to dismiss and motion by FDA for preliminary injunction, both parties moved for summary judgment.

[Holding:] The District Court, Timothy J. Corrigan, J., held that Federal Food, Drug, and Cosmetic Act (FDCA) did not give FDA enforcement authority to prevent state-licensed pharmacists from bulk compounding medications for non food-producing animals.

Defendant's motion granted.

West Headnotes (13)

[1] Federal Civil Procedure
Issues of law

When the only question a court must decide is a question of law, summary judgment may be granted.

Cases that cite this headnote

[2] Federal Civil Procedure
By both parties

The principles governing summary judgment do not change when the parties file cross-motions for summary judgment, and when faced with cross-motions, the court must determine whether either of the parties deserves judgment as a matter of law on the undisputed facts.

Cases that cite this headnote

[3] Health
Pharmacists

Under Florida law, traditional compounding from bulk substances is an approved part of the practice of pharmacy. Fla.Admin.Code Ann. r. 64B16–27.700(1); r. 64B16–27.1001(2).

Cases that cite this headnote

[4] Health
Animal drugs

Provision of Federal Food, Drug, and Cosmetic Act (FDCA) prohibiting introduction of any new drug without approval from Food and Drug Administration (FDA) did not give FDA enforcement authority to prevent state-licensed pharmacists from bulk compounding medications for non food-producing animals; though "new animal drug" definition in FDCA afforded FDA license to enforce against pharmacists who manufactured in guise of compounding, Congress did not give FDA authority to enjoin traditional pharmacy compounding of animal drugs, a practice never before regulated by federal agency and never mentioned in FDCA, and even if Congress had implicitly delegated authority to FDA to regulate traditional pharmacy compounding of animal medications, court would not afford *Chevron* deference to FDA interpretation of statute, as FDA had never promulgated regulations to this effect through notice-and-comment rule-making, and statutory interpretation by FDA lacked power to persuade. Federal Food,

Drug, and Cosmetic Act, §§ 201(v)(1), 505(a), 21 U.S.C.A. §§ 321(v)(1), 355(a).

2 Cases that cite this headnote

[5] **Administrative Law and Procedure**
Statutory basis and limitation
Constitutional Law
Standards for guidance

The "elephant-in-mouseholes doctrine" recognizes that Congress does not delegate decisions of economic and political significance to an agency in a vague or cryptic fashion; that is, it does not hide elephants in mouseholes.

Cases that cite this headnote

[6] **States**
State police power

The "plain statement rule" requires that Congress speak in clear terms when displacing traditional state regulation of a particular practice.

Cases that cite this headnote

[7] **Criminal Law**
Liberal or strict construction;rule of lenity

The "rule of lenity" requires that when a statute carries criminal penalties, any ambiguities must be interpreted in the defendant's favor to avoid prohibiting more conduct or punishing more severely than Congress intended.

Cases that cite this headnote

[8] **Administrative Law and Procedure**
Administrative construction

An agency's interpretation of its own ambiguous regulation promulgated pursuant to a congressional grant of authority is controlling unless plainly erroneous or inconsistent with the regulation.

Cases that cite this headnote

[9] **Health**
Purpose and construction of statutes

The primary purpose of the Federal Food, Drug, and Cosmetic Act (FDCA) is to protect and safeguard consumers from dangerous products. Federal Food, Drug, and Cosmetic Act, § 1, 21 U.S.C.A. § 301.

Cases that cite this headnote

[10] **Health**
Animal drugs

Application of elephants-in-mouseholes doctrine was warranted to construe term "new drug," as used in the Federal Food, Drug and Cosmetic Act (FDCA), as not including bulk compounded animal drugs, warranting further review by district court to determine whether FDCA was ambiguous in such a way as to make Food and Drug Administration's (FDA) decision to prevent state-licensed pharmacists from engaging in bulk compounding of animal drugs worthy of deference under the second step of *Chevron*; it was not clear that Congress meant to hide the elephant of Food and Drug Administration's regulation of traditional pharmacy compounding in the mousehole of the FDCA new drug approval process, and despite the literal language of the statute, Congress had not directly and plainly said that the traditional pharmacy compounding of animal drugs must meet the requirements of the new drug approval provisions of the FDCA. Federal Food, Drug, and Cosmetic Act, § 201(p), (v)(1), 21 U.S.C.A. § 321(p), (v)(1).

2 Cases that cite this headnote

[11] **Administrative Law and Procedure**
Plain, literal, or clear meaning; ambiguity

Where Congress has not entered a direct regulatory command to a federal agency by

the plain language of a statute, further review is warranted to determine whether the statute is ambiguous in such a way as to make the agency's decision regarding enforcement of the statute worthy of deference under the second step of *Chevron*.

Cases that cite this headnote

[12] Administrative Law and Procedure
Plain, literal, or clear meaning; ambiguity

When Congress has generally conferred authority on an agency through a statute, Congress expects the agency to speak with the binding authority of law when it addresses ambiguity in the statute or fills a space in the enacted law, even if there was no congressional intent for a particular result.

Cases that cite this headnote

[13] Health
Animal drugs

Rule of lenity applied to resolve ambiguity in provision of Federal Food, Drug, and Cosmetic Act (FDCA) prohibiting introduction of any new drug without approval from Food and Drug Administration (FDA) in favor of state-licensed pharmacists who bulk compounded medications for non food-producing animals, rather than FDA; compounding of one non food-producing medication from bulk ingredients subjected state-licensed pharmacist, whether pharmacist's practice consisted of large, interstate operation, or Mom-and-Pop shop, to criminal penalties of FDCA, and such standard openly invited arbitrary enforcement, which was antithetical to system of criminal justice. Federal Food, Drug, and Cosmetic Act, §§ 301, 505(a), 21 U.S.C.A. §§ 331, 355(a).

Cases that cite this headnote

West Codenotes

Recognized as Unconstitutional
21 U.S.C.A. § 353a

Attorneys and Law Firms

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Alan R. Dial, Ashley C. Parrish, Jeffrey S. Bucholtz, Mark S. Brown, King & Spalding LLP, Washington, DC, Edward L. Birk, Jeptha Fowlkes Barbour, Marks Gray, PA, Paul E. Bueker, Law Offices of Fred Tromberg, Jacksonville, FL, Michael E. Dean, Dean Law Firm, LLC, Ocala, FL, for Defendants.

ORDER

TIMOTHY J. CORRIGAN, District Judge.

In the seventy-plus years since Congress created the Food and Drug Administration, the FDA has never before sought to enjoin a state-licensed pharmacist from engaging in the traditional practice of bulk compounding of animal drugs. Here, the FDA seeks just such an injunction. This case of first impression implicates matters of statutory construction, federalism, and the proper deference to be afforded to the FDA in interpreting its enabling statute.

I. Facts and Procedural Posture

This statutory injunction proceeding is brought by the United States of America, on behalf of the FDA, against defendants Franck's Lab, Inc. d/b/a Franck's Compounding Lab ("Franck's") and Paul W. Franck, Franck's owner and CEO. Franck's is a pharmacy located in Ocala, Florida which compounds and distributes a wide variety of drugs for both humans and animals to customers across the United States.

The facts of this case are straightforward and largely undisputed. Mr. Franck, a Florida-licensed pharmacist in good standing since 1981, opened an independent pharmacy practice in Archer, Florida in 1983. Over the next several years, Franck expanded his practice by purchasing or opening additional retail pharmacies, including a location in Ocala in 1985. That same year, Franck began to compound medications at the

Ocala location for humans and "non food-producing animals" (such as horses). The Ocala pharmacy was later expanded into two practices ***1212** which now comprise Franck's: Franck's Lab, which operates as a compounding pharmacy, and Franck's Pharmacy, which is a traditional retail pharmacy. At the time the FDA instituted this action, Franck's employed approximately 65 individuals full-time.

Animal and veterinary drug compounding comprises roughly 40 percent of Franck's Lab's business, while human drug compounding accounts for the remaining 60 percent.[1] Franck's compounds the majority of its animal medications from "bulk" active ingredients,[2] which it receives from suppliers outside the state of Florida. The company also receives prescription orders from customers outside Florida and ships its compounded products to those out-of-state customers. Franck's holds a valid pharmacy license in each of the 47 states in which it is required to do so, and, nationwide, fills approximately 37,000 animal drug prescriptions per year.

The FDA first inspected Franck's compounding facilities between September 29 and October 4, 2004 and, in January 2005, issued a warning letter expressing concern that Franck's was impermissibly manufacturing drugs. (Doc. 17–1, Declaration of Emma Singleton[3] ("Singleton Dec."), Ex. E.) Among the FDA's concerns were: (i) Franck's practice of compounding veterinary drugs using bulk active pharmaceutical ingredients; (ii) that a number of those drugs "appear[ed] to be compounded outside the context of a valid veterinarian-client-patient relationship;" and (iii) that Franck's was compounding drugs where an approved drug would adequately treat the animal. (*Id.* at 1–2.)

Franck's responded by letter dated January 27, 2005, asserting its intention to be in full compliance with all FDA requirements. (*Id.* Ex. F.) However, Franck's also expressed disagreement with the FDA's position that bulk compounding of animal drugs was *per se* unlawful and noted that "[s]tate law and good compounding practices ... allow bulk compounding as long as there is a valid patient physician (veterinarian) relationship." (*Id.* at 1.) Franck's further argued that, because "the FDA allows compounding by bulk chemicals for human use, ... the same should apply to veterinary compounding." (*Id.*) Despite the disagreement, Franck's pledged: (1) to dispense compounded veterinary drugs only to licensed veterinarians pursuant to a "valid patient-veterinarian relationship"; (2) to compound from bulk only those drugs that were commercially unavailable; and (3) to place warning labels on its products to make clear that its compounds were "not to be used on food producing animals."[4] (*Id.* at 1–2.) In closing, Franck's stated:

> Again, it is Franck's intention to comply immediately and completely with any and all FDA and other legal requirements, and welcomes [sic] the FDA's involvement in these matters. I have tried to the best of my ability to address each item of concern in your letter. If I ***1213** have fallen short on anything, if you have additional concerns which were not set forth in your letter, or if you have any other questions or concerns, please contact me immediately and I will see to it that we respond immediately, and to your complete satisfaction.
>
> (*Id.* at 2.) FDA did not respond to Franck's' letter and did not take any further action against the pharmacy at that time.

In April 2009, a veterinarian commissioned Franck's to compound an injectable solution of the prescription drug Biodyl for the Venezuelan national polo team. Due to a mathematical error in the conversion of an ingredient (which went unnoticed by the prescribing veterinarian), the compounded medication was too potent and 21 polo horses died. The incident was thoroughly investigated by the Florida Board of Pharmacy, which imposed fines and reprimanded Franck's for the misfilled prescription.[5] Despite the reprimand, the Board voted to allow Franck's to continue its pharmacy compounding practice without restriction, and Franck's remains in good standing in Florida. The FDA has acknowledged that it was a mathematical error, as opposed to "faulty bulk drugs," which caused the death of the polo ponies. (Doc. 47 at 27.)

Though the Florida Board of Pharmacy had investigated and resolved the matter to its satisfaction, the Venezuelan polo pony incident prompted the FDA to reinspect Franck's facilities three times: May 4–20, 2009; June 18–23, 2009; and December 1–4, 2009. Subsequent to the May inspection, the FDA issued Franck's a Form FDA 483 which contained five specific observations, none of which identified bulk compounding of animal drugs as a concern. (Singleton Dec. Ex. B.)[6]

Franck's responded to the Form 483 by letter dated June 12, 2009. (*Id.* Ex. C.) The letter stated that the pharmacy had "carefully considered the [FDA's] observations" and used them "to help further strengthen our operations." (*Id.* at 1.) However, Franck's noted that:

> the observations that FDA has outlined involve pharmacy practices that we must strenuously assert are regulated by the Florida Department of Health and Board of Pharmacy. We are concerned that FDA is attempting to assert authority over Franck's Pharmacy that it reserves for drug manufacturers. Put simply, we are a compounding pharmacy that fills prescriptions to meet the needs of individual patients; we are not a drug manufacturer....
>
> The events that are the subject of the FD–483 observations [i.e., the polo pony incident] represent classic, traditional compounding. Franck's was filling a single prescription from a veterinarian specifically and solely for that veterinarian's patients. This was prototypical compounding ....
>
> The Florida Department of Health [conducted] its own inspection and [viewed] the incident as one relating to compounding. Even the FDA investigators orally acknowledged that the activities in question constituted compounding ....
>
> ***1214** Franck's has been compounding human and veterinary drugs for more than 25 years to meet the special needs of doctors, veterinarians, and patients. We take both our obligations to our patients and our regulatory responsibilities very seriously.

(*Id.* at 2–4.) Without further response or discussion, FDA initiated this action in April of 2010, seeking to enjoin Franck's practice of distributing animal drugs compounded from bulk substances.[7]

After Franck's moved to dismiss the complaint (Doc. 13), the FDA sought a preliminary injunction (Doc. 16). The Court heard oral argument on August 18, 2010 (Doc. 43), the record of which is incorporated by reference. The Court subsequently denied both motions (Doc. 44) and, at the parties' request, postured the case for resolution via dispositive motions (Doc. 53). The parties then fully developed the record, each submitting declarations and other materials,[8] as well as a Joint Stipulation of Undisputed Facts (Doc. 55). Thereafter, the parties filed extensive cross-motions for summary judgment and responses thereto (Docs. 54, 56, 59, 60). The Court heard lengthy oral argument on the parties' cross-motions on February 24, 2011 (Doc. 61), the record of which is incorporated by reference.

II. The Record Allows for Disposition on Cross–Motions for Summary Judgment

The FDA acknowledges that this is the first time it has sought to enjoin a state-licensed pharmacist from bulk compounding of animal medications. Further, through its development of the record and posturing of this case, the FDA has made clear that the legal violation it asserts is not contingent on any fact-specific grounds unique to Franck's. Rather, the FDA has taken the bright-line position that *any* compounding of animal medications from bulk substances violates its enabling statute, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, *et seq.* ("FDCA"), even when conducted by a state-licensed pharmacist for an individual animal patient pursuant to a valid veterinary prescription. Franck's admits that it routinely engages in this practice, but contends that it does not violate the FDCA.

The FDA's evidentiary support for this action is primarily contained in two declarations that describe: (i) Franck's alleged violative history (as set forth *infra, see* Singleton Dec.);[9] and (ii) the FDA's rationale ***1215** and asserted authority for regulating animal drug compounding, (see Doc. 17–2, Declaration of Dr. William Flynn[10] ("Flynn Dec.")). In response, Franck's submitted a number of declarations from veterinarians, pharmacists, and other expert and fact witnesses relating to, *inter alia:* (i) the FDA's historical acceptance of and shifting approach towards "traditional pharmacy compounding"; (ii) their understanding of the FDA's role in regulating the practice; (iii) the necessity of bulk compounding to provide life-saving treatment for non food-producing animal patients; (iv) the ubiquity of the practice of compounding animal drugs from bulk; and (v) the industry standards for quality control in the preparation of such compounded medications. (*See* Doc. 28, Declaration of Paul W. Franck ("Franck Dec."); Doc. 29, Declaration of Gigi S. Davidson[11] ("Davidson Dec."); Doc. 30, Declaration of Dr. Loyd V. Allen[12] ("Allen Dec."); Powers Dec.; Doc. 32, Declaration of Kevin Stoothoff, D.V.M.[13] ("Stoothoff Dec."); Doc.

33, Declaration of Rick Pelphrey, D.V.M.[14] ("Pelphrey Dec."); Doc. 35, Declaration of Sheldon T. Bradshaw[15] ("Bradshaw Dec.").)

Though the FDA had ample opportunity to dispute these assertions, it chose not to do so, resting instead on its position that compounding animal drugs from bulk—which Franck's admits it does—constitutes a *per se* violation of the FDCA. As a result, the statements contained in Franck's' declarations are largely uncontroverted in the record, and where appropriate, the Court treats them as such.[16]

[1] **[2]** Because no material facts are in dispute, the parties' cross-motions present this Court with a pure question of law. "When the only question a court must decide is a question of law, summary judgment may be granted." *Saregama India Ltd. v. Mosley,* 635 F.3d 1284, 1290 (11th Cir.2011) (citing *Cook ex rel. Estate of Tessier v. Sheriff of Monroe Cnty.,* 402 F.3d 1092, 1120 (11th Cir.2005)) ("A summary ***1216** judgment should not be granted unless the facts are so crystallized that nothing remains but questions of law"). "The principles governing summary judgment do not change when the parties file cross-motions for summary judgment. When faced with cross-motions, the Court must determine whether either of the parties deserves judgment as a matter of law on the undisputed facts." *T–Mobile South LLC v. City of Jacksonville, Florida,* 564 F.Supp.2d 1337, 1340 (M.D.Fla.2008).

III. Background

A. Compounding and Compounding from Bulk Substances

Compounding is a process by which a pharmacist combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual human or animal patient. *Thompson v. W. States Med. Ctr.,* 535 U.S. 357, 360–61, 122 S.Ct. 1497, 152 L.Ed.2d 563 (2002); *Med. Ctr. Pharm. v. Mukasey,* 536 F.3d 383, 387 (5th Cir.2008).[17] Compounding is "a traditional component of the practice of pharmacy, and is taught as part of the standard curriculum at most pharmacy schools." *W. States,* 535 U.S. at 361, 122 S.Ct. 1497 (internal citations omitted). Because the practice of pharmacy is state-governed, the States, including Florida, regulate compounding as part of their regulation of pharmacists. *Id.*[18]

Under Florida law, pharmacists may compound medications when they are prescribed for individual patients by a licensed medical practitioner (i.e., a veterinarian), or in anticipation of prescriptions based on routine, regularly observed prescribing patterns.[19] This "triad" relationship among veterinarian, patient, and pharmacist envisions a compounding pharmacist working collaboratively with a veterinarian to provide a medication tailored to an animal patient's specific and individualized needs. (*See* Davidson Dec. ¶ 36.) The pharmacist-prescriber-patient relationship forms the basis of what is commonly known as "traditional pharmacy compounding."[20]

***1217** "Compounding is typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product." *W. States,* 535 U.S. at 361, 122 S.Ct. 1497. When a drug is not commercially available, or the commercially available drug is unsuitable for a particular patient, compounding is often the only way for a human or animal patient to obtain necessary medication for the safe and effective treatment of their condition. *See id.* at 369, 122 S.Ct. 1497. This is especially so for non food-producing animals because limited commercially available products exist and the available products are often inadequate due to the animal patient's size, species, and/or intolerance to active ingredients. (Davidson Dec. ¶ 35); *cf. U.S. v. 9/1 Kg. Containers, More or Less, of an Article of Drug for Veterinary Use,* 854 F.2d 173, 174 (7th Cir.1988) ("We must take it as given that for significant [animal] diseases there are no effective FDA-approved drugs.... For the principal diseases of non-food animals ... there are few, if any, approved remedies").[21]

A pharmacist can compound a medication requested by the prescribing veterinarian from either a finished drug product or from bulk drug substances. (Flynn Dec. ¶ 15.) Between the two, compounding from bulk substances has become the "widely preferred" method among veterinarians due to "concerns about the quality, safety, and efficacy of animal medications compounded from finished products." (Allen Dec. ¶¶ 17, 24.) Pharmacists also favor compounding from bulk because use of bulk ingredients ensures that the compounded medicine is of

the expected purity,[22] potency,[23] and quality; further, it is ***1218** often not practical[24] or possible[25] to compound a medically necessary animal drug from an FDA-approved finished drug product. (*Id.* ¶¶ 17, 23–25.) In addition, the standards for potency and purity of compounded medications required by the United States Pharmacopeia ("USP"), which the original FDCA recognized as its "official compendium," Food, Drug and Cosmetic Act of 1938, Pub.L. No. 75–717, 52 Stat. 1040 ("1938 FDCA") § 201(j), are more readily obtained using bulk ingredients.[26] (Allen Dec. ¶¶ 27–32.) As a result, compounding from a finished drug product "is more likely to result in a compounded preparation outside of the [USP's] required potency and purity specifications than compounding from a bulk ingredient." (*Id.* ¶ 29.)

[3] Under Florida law, traditional compounding from bulk substances is an approved part of the practice of pharmacy.[27] ***1219** As a result, many, if not all, compounding pharmacies in Florida compound drug products from bulk ingredients. (Powers Dec. ¶ 24.)[28] Florida is not an outlier in this regard; the practice of compounding from bulk ingredients is expressly recognized by many states and is a "widespread practice performed by the majority of licensed compounding pharmacy professionals throughout the country, and has been for decades." (Allen Dec. ¶ 23.)[29]

B. The FDA's Regulation of Compounding

1. From 1938 to 1992

The history of the FDA's regulation of pharmacy compounding has been reviewed several times, most notably by the Supreme Court in *Western States,* 535 U.S. at 360–66, 122 S.Ct. 1497, and the Fifth Circuit in *Medical Center,* 536 F.3d at 387–91. As the Supreme Court recounted (emphasis and footnotes added):

> The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), 21 U.S.C. §§ 301–397, *regulates drug manufacturing, marketing, and distribution.* Section 505(a) of the FDCA provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed [with the Food and Drug Administration] is effective with respect to such drug." 21 U.S.C. § 355(a). "[N]ew drug" is defined by § 201(p)(1) of the FDCA, 52 Stat. 1041, as amended, 76 Stat. 781, as "[a]ny drug ... not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p).[30] The FDCA invests the Food and Drug Administration (FDA) with the power to enforce its requirements. § 371(a).[31]

***1220** *For approximately the first 50 years after the enactment of the FDCA, the FDA generally left regulation of compounding to the States.* Pharmacists continued to provide patients with compounded drugs without applying for FDA approval of those drugs. The FDA eventually became concerned, however, that some pharmacists were manufacturing and selling drugs under the guise of compounding, thereby avoiding the FDCA's new drug requirements. In 1992, in response to this concern, the FDA issued a Compliance Policy Guide, which announced that the *"FDA may, in the exercise of its enforcement discretion, initiate federal enforcement actions ... when the scope and nature of a pharmacy's activities raises the kinds of concerns normally associated with a manufacturer and ... results in significant violations of the new drug, adulteration, or misbranding provisions of the Act."* Compliance Policy Guide 7132.16 (hereinafter [1992] Guide).[32] The Guide explained that the "FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner," and that *such activity was not the subject of the Guide.* The Guide said, however, "that while retail pharmacies ... are exempted from certain requirements of the [FDCA], they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions" of the FDCA. It stated that the "FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing, distributing, and promoting unapproved new drugs for human use in a manner that is *clearly outside the bounds of traditional pharmacy practice and that constitute violations of the [FDCA].*" The Guide expressed concern that drug products "manufactured and distributed in commercial amounts without [the] FDA's prior approval" could harm the public health.

> In light of these considerations, the Guide announced that it was FDA policy to permit pharmacists to compound drugs after receipt of a valid prescription for an individual patient or to compound drugs in "very limited quantities" before receipt of a valid prescription if they could document a history of receiving valid prescriptions "generated solely within an established professional practitioner-patient-pharmacy relationship" and if they maintained the prescription on file as required by state law. Compounding in such circumstances was permitted as long as the pharmacy's activities did not raise "the kinds of concerns normally associated with a manufacturer."
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> ***1221** *W. States,* 535 U.S. at 361–63, 122 S.Ct. 1497 (emphasis added and citations omitted).

After acknowledging that the FDA would "generally continue to defer to state and local officials[']regulation of the day-to-day practice of retail pharmacy and related activities," the 1992 Guide listed nine non-inclusive activities that the FDA believed would improperly cross the line between "pharmacist" and "manufacturer" and thus would prompt the FDA to "initiate federal enforcement actions" in the "exercise of its enforcement discretion." 1992 Guide at 4–5.[33] The practice of compounding drugs from bulk substances was not among the nine prohibited practices, though the concern that large-scale compounding from bulk might be indicative of manufacturing was mentioned elsewhere in the 1992 Guide.[34]

2. AMDUCA

In 1994, Congress passed the Animal Medicinal Drug Use Clarification Act ("AMDUCA"), which amended the FDCA to permit certain off-label uses of FDA-approved human and animal drugs in the treatment of animals. 21 U.S.C. §§ 360b(a)(4) and (a)(5).[35] Under AMDUCA, the off-label or extra-label use of an already approved new animal or new human drug prescribed by a licensed veterinarian in the context of a valid pharmacist-prescriber-patient relationship does not require approval under the FDCA's "new animal drug" provisions, and thus does not cause the drug to become "adulterated." *Id.* AMDUCA authorized the FDA to promulgate regulations which "establish the conditions" for such off-label use. *Id.* §§ 360b(a)(4)(A), 5(B).

Though Congress made no mention of either compounding or bulk drugs in AMDUCA, the FDA regulations promulgated to implement AMDUCA explicitly reference both. Section 530.13, entitled "Extralabel use from compounding of approved new animal and approved human drugs," provides that "[t]his part applies to *compounding of a product* from approved animal or human drugs by a veterinarian ***1222** or a pharmacist on the order of a veterinarian within the practice of veterinary medicine. *Nothing in this part shall be construed as permitting compounding from bulk drugs.*" 21 C.F.R. § 530.13(a) (emphasis added). Despite this language, the regulations do not purport to regulate the practice of compounding, and instead refer parties to FDA's non-binding guidance documents on the subject. *See id.* § 530.13(c) ("Guidance on the subject of compounding may be found in guidance documents issued by FDA").[36]

3. The 1996 Guide

In 1996, the FDA published notice in the Federal Register inviting public comment on a Compliance Policy Guide outlining the agency's non-binding "policy and regulatory guidelines" with respect to the compounding of animal drugs by veterinarians and pharmacists. 61 Fed.Reg. 34,849, 34,849 (1996) ("1996 Guide"). The 1996 Guide noted that the FDCA "does not distinguish compounding from manufacturing or other processing of drugs for use in animals," nor does it exempt pharmacists and veterinarians from the FDCA's new drug approval provisions. *Id.* at 34,850. While the FDA "acknowlege[d] the use of compounding within certain areas of veterinary practice," it also asserted that "compounding allowed under the [FDCA] is limited to the preparation of drug products which do not meet the definition of new animal drugs" and that "[i]n the absence of an approved new animal drug application (NADA), the compounding of a new animal drug from ... a bulk drug, results in an adulterated new animal drug...." *Id.*[37]

Despite this broad assertion of the FDA's authority, the 1996 Guide recognized a legitimate place for compounding. Specifically, the Guide provided that "compounding by a licensed pharmacist or veterinary practitioner, when the criteria described in this document are met, [and] within the confines of a legitimate practice" would constitute "compounding ordinarily not subject to regulatory action." *Id.*[38] With this background, the

1996 Guide's "Policy" section began with the ***1223** acknowledgment that "[c]ircumstances exist when it may be necessary for a veterinarian to compound, or direct for a pharmacist to compound, an article that will result in an unapproved animal drug." *Id.* at 34,851. In such circumstances, the FDA recognized that there was "occasionally a need to utilize ... bulk drug substances[ ] for compounding into an appropriate dosage form." *Id.* The FDA would thus condone compounding animal drugs from bulk where: (1) a "legitimate medical need [wa]s identified"; (2) there was an "appropriate dosage regimen" for the patient's species, age, size, or medical condition; and (3) there was "no marketed approved animal drug" that "may treat the condition diagnosed in the available dosage form." *Id.* Under these conditions, the FDA would ordinarily not exercise its enforcement authority against a compounding pharmacist so long as the medication was dispensed within the confines of a pharmacist-prescriber-patient relationship; the drug was adequately labeled to ensure proper use; and the pharmacist adhered to the National Association of Boards of Pharmacy Good Compounding Practices, or to equivalent state good compounding regulations. *Id.* The FDA closed its policy pronouncement with the following: "Veterinarians and pharmacists who compound or prescribe compounded medicaments and pharmacists who compound medicaments according to these guidelines criteria set out above would be considered to be engaged in extemporaneous compounding not ordinarily subject to regulatory action." *Id.*

The 1996 Guide then listed thirteen situations which would "likely indicate compounding subject to regulatory action." *Id.* "Compounding from bulk drugs for use in *food* animals," with certain limited exceptions, was among the listed scenarios. *Id.* (emphasis added). [39] However, "[c]ompounding from bulk drug substances for use in nonfood animals" was expressly identified as a "compounding situation [which] would not ordinarily be considered for regulatory action." *Id.* at 34,852. [40]

4. FDAMA & Western States

In 1997, "in a move the Pharmacies call a reaction to the FDA's 1992 [Guide] and the FDA characterizes as a confirmation of it, Congress amended the FDCA by enacting the Food And Drug Modernization Act of 1997 ("FDAMA"), Pub.L. No. 105–115, 111 Stat. 2296 (codified as amended at 21 U.S.C. § 353a (2000))." *Med. Ctr.,* 536 F.3d at 391. [41] Expressly addressing "pharmacy compounding," FDAMA, which applies only to human drugs, provides that the FDCA's new drug approval, adulteration, and misbranding provisions "*shall not apply* to a drug product if the drug product ***1224** is compounded" pursuant to certain guidelines. 21 U.S.C. § 353a(a) (emphasis added). [42] As summarized by the Supreme Court in *Western States,* those guidelines are as follows:

> First, [compounded drugs] *must be compounded by a licensed pharmacist or physician in response to a valid prescription for an identified individual patient, or, if prepared before the receipt of such a prescription, they must be made only in "limited quantities" and in response to a history of the licensed pharmacist's or physician's receipt of valid prescription orders for that drug product within an established relationship between the pharmacist, the patient, and the prescriber.* 21 U.S.C. § 353a(a). Second, the compounded drug must be made from approved ingredients that meet certain manufacturing and safety standards, §§ 353a(b)(1)(A)-(B), [43] and the compounded drug may not appear on an FDA list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or ineffective, § 353a(b)(1)(C). Third, the pharmacist or physician compounding the drug may not "compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product." § 353a(b)(1)(D). Fourth, the drug product must not be identified by the FDA as a drug product that presents demonstrable difficulties for compounding in terms of safety or effectiveness. § 353a(b)(3)(A). Fifth, in States that have not entered into a "memorandum of understanding" with the FDA addressing the distribution of "inordinate amounts" of compounded drugs in interstate commerce, the pharmacy, pharmacist, or physician compounding the drug may not distribute compounded drugs out of state in quantities exceeding five percent of that entity's total prescription orders. § 353a(b)(3)(B). Finally ... the prescription must be "unsolicited," § 353a(a), and the pharmacy, licensed pharmacist, or licensed physician compounding the drug may "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," § 353a(c).

Western States, 535 U.S. at 364–65, 122 S.Ct. 1497 (emphasis and footnote added).

"Shortly after passage of FDAMA, however, trouble arose. In 2002, in *Western States,* 535 U.S. at 368–77, 122 S.Ct. 1497, the Court invalidated the advertising-related provisions of FDAMA, affirming the Ninth Circuit's holding that those portions were unconstitutional restrictions on commercial speech." *Med. Ctr.,* 536 F.3d at 391.[44] Interestingly, in arguing (unsuccessfully) ***1225** that FDAMA's advertising provisions advanced a substantial government interest, the Secretary of the U.S. Department of Health and Human Services asserted the importance of

> "preserv[ing] the availability of compounded drugs for those individual patients who, for particularized medical reasons, cannot use commercially available products that have been approved by the FDA.... *[B]ecause obtaining FDA approval for a new drug is a costly process, requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment." The Government argues that eliminating the practice of compounding drugs for individual patients would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages.*
>
> *W. States,* 535 U.S. at 368–69, 122 S.Ct. 1497 (emphasis added). The Supreme Court recognized the importance of these competing concerns; i.e., protecting the new drug approval process while simultaneously permitting traditional compounding's continued existence:
>
> > Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding *so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process.* Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so *requiring such testing would force pharmacists to stop providing compounded drugs.* Given this, the Government *needs to be able to draw a line between small-scale compounding and large-scale drug manufacturing.* That line must distinguish compounded drugs produced on *such a small scale* that they could not undergo safety and efficacy testing from drugs produced and sold on a large enough scale that they could undergo such testing and therefore must do so.
>
> *Id.* at 369–70, 122 S.Ct. 1497 (emphasis added). The Court ultimately found that conditioning an exemption from the FDA approval process on refraining from advertising was an inappropriate way to draw the "small-scale" versus "large-scale" distinction. *Id.* at 370–71, 122 S.Ct. 1497. In so holding, however, the Court noted that "[s]everal non-speech-related means of drawing a line between compounding and large-scale manufacturing might be possible here. First, it seems that the Government could use the very factors the FDA relied on to distinguish compounding from manufacturing in its 1992 Guide." *Id.* at 372, 122 S.Ct. 1497.[45] The Court further ***1226** noted that it had been provided no reason why these factors, "alone or in combination, would be insufficient to prevent compounding from occurring *on such a scale as to undermine the new drug approval process.*" *Id.* at 373, 122 S.Ct. 1497 (emphasis added).

5. The 2002 and 2003 Guides and Beyond

In the wake of *Western States,* the FDA issued revised Compliance Policy Guides addressing compounding of human and animal drugs.[46] *See Med. Ctr.,* 536 F.3d at 391. Like the 1992 and 1996 Guides before them, the 2002 and 2003 Guides assert that compounded human and animal drugs are not exempt from the FDCA's new drug approval, adulteration, or misbranding provisions. *Id.* And the updated Guides continue to assure pharmacists that the FDA will use its enforcement discretion against a compounding pharmacy only where the pharmacy's activities raise the kinds of concerns normally associated with manufacturing. *Id.* Despite these overarching parallels, however, the new Guides make a number of policy departures from their predecessors.

In the 2002 Guide, which addresses human drugs, the FDA asserts that "all of [FDAMA] is now invalid" in light of the Ninth Circuit's severability holding in *Western States.* 2002 Guide at 2. Despite this, the 2002 Guide appears to embrace FDAMA's effusive attitude towards traditional pharmacy compounding.[47] The focus of the guidance is the FDA's desire to eradicate improper manufacturing, which, with regard to bulk drugs, is framed as an issue of scale:

> FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities ***1227** are the focus of this guidance. Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. *For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of receiving a valid prescription for them.* Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship. Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers.
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> 2002 Guide at 3 (emphasis added). Apart from its use in the sentence "some firms receive and use large quantities of bulk drugs," the word "bulk" appears only one other time in the 2002 Guide. A compounder's use of bulk ingredients that are not "components of FDA approved drugs" is listed as a factor FDA will consider in bringing an enforcement action. *Id.* at 4.

The 2003 Guide, which addresses animal drug compounding, was, according to the FDA, issued "to ensure the consistency of its policies with regard to compounding of drugs intended for use in humans and in animals." 2003 Guide at 2–3. From the outset, however, the 2003 Guide strikes a decidedly more hostile tone toward compounding than its human drug counterpart (as well as its 1996 predecessor):

> There is a potential for causing harm to public health and to animals when drug products are compounded, distributed, and used in the absence of adequate and well-controlled safety and effectiveness data or adherence to the principles of contemporary pharmaceutical chemistry and current good manufacturing practices. Use of compounded drugs in animals can result in adverse reactions and animal deaths.

Id. at 2. Unlike the 1996 Guide and the AMDUCA regulations, the 2003 Guide makes no distinction between food and non food-producing animals.[48] Further, the 2003 Guide contains no discussion about permitted compounding practices (apart from the use of extra-label drugs under AMDUCA), and instead announces that the FDA intends to target the compounding of animal drugs conducted "in a manner that is clearly outside the bounds of *traditional pharmacy practice* ... (e.g., compounding that is *intended to circumvent* the drug approval process and provide for the mass marketing of products that have been produced with little or no quality control or manufacturing standards to ensure the purity, potency, and stability of the product)." 2003 Guide at 3 (emphasis added).[49]

***1228** However, the most noticeable departure in the 2003 Guide is the FDA's policy regarding the use of bulk drug substances in compounded animal medications. While the 1996 Guide acknowledged the occasional utility of compounding from bulk, the circumstances under which doing so would not subject a pharmacist to potential regulatory action, and the permissibility of the practice for non food-producing animals, such statements are absent—without explanation—from the 2003 Guide. And despite the 2002 Guide's allowance of compounding from bulk for human drugs so long as the bulk ingredients are FDA-approved, the 2003 Guide lists "[c]ompounding finished drugs [for animals] ... from bulk substances" among the factors which "raise[ ] the kind[ ] of concern normally associated with a manufacturer." *Id.* at 5.

Attached to the 2003 Guide is an appendix entitled "Appendix A: List of Bulk Drug Substances for Compounding and Subsequent Use in Animals to Which the CVM Would Not Ordinarily Object." *Id.* at 7. The appendix lists nine such substances, but provides no explication or rationale of the FDA's methodology for the approval of the listed substances to the exclusion of others. Nor does the 2003 Guide draw any distinctions based upon the scale of bulk compounding activity, implying that a pharmacist who compounds one animal medication from bulk for a non food-producing animal has committed a *per se* violation of the FDCA. Thus, under the 2002 and 2003 Guides, *a pharmacist who compounds medication from bulk for ingestion by a horse is akin to a manufacturer and subject to an FDA enforcement action, while the same pharmacist compounding medication from bulk for ingestion by the human rider of that horse is not.* This is so despite the 2002 Guide's assertion that "all of [FDAMA] is invalid" and the 2003 Guide's stated intent to maintain consistency in the FDA's policies regarding regulation of human and animal drugs. [50]

Because the FDA considered the 2003 Guide's policy changes to be "minor," the agency did not publish a notice in the Federal Register or invite public comment prior to issuing it. 21 C.F.R. § 10.115 (setting forth "good guidance practices" for FDA to follow in developing, issuing and using guidance documents, which include notice-and-comment procedures for guidance documents which "[s]et forth changes in interpretation or policy that are of more than a minor nature"). Having ***1229** been deprived the opportunity for public comment, Franck's and a number of other compounding pharmacists, veterinarians, and related associations (including the Small Business Association's Office of Advocacy), wrote letters to Congress and to the FDA's CVM, expressing concern that the policies outlined in the 2003 Guide "would cause many animal patients to suffer needlessly." (Davidson Dec. ¶ 48.) In turn, more than seventy members of Congress wrote separately to the FDA, reiterating the policy concerns of the veterinarians and pharmacists. (*Id.* at Ex. 6.) The Congressmen called it "disconcerting" that the Guide was "put into effect without the opportunity for public review and comment by stakeholders" and therefore asked "[FDA] to withdraw it and issue a revised [Guide] for public comment." (*Id.*)

In September 2004, the FDA responded to the various complaints by issuing the following notice:

> FDA is announcing its intention to draft and publish for public comment a revised Compliance Policy Guide (CPG) on veterinary pharmaceutical compounding. FDA anticipates that the draft CPG will be available for comment in the Fall of 2004.
>
> The current CPG, published in July 2003, describes FDA's present thinking on what types of veterinary compounding might be subject to enforcement action. *FDA has received numerous letters from veterinarians, pet owners, compounding pharmacists, and associations expressing concern that the CPG lacks sufficient clarity on the circumstances in which veterinary compounding, particularly from bulk drugs, would be permitted. Many of the letters also disagreed with the current policy, stating that it was not within FDA's legal authority, and complained about the lack of prior public comment.* After meeting with several groups and considering the comments in the letters it has received FDA concluded that issuing a revised CPG is appropriate.
>
> When it is available, the draft CPG will be posted on FDA's Center for Veterinary Medicine (CVM) Website and a notice of availability will be published in the Federal Register.

CVM Updates: *FDA to Revise Its Compliance Policy Guide on Veterinary Compounding,* September 1, 2004, *available at* http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048425.htm (last visited September 12, 2011) (emphasis added).

Despite its promise to do so, the FDA did not propose or issue any form of revised guidance in the fall of 2004.
In two separate letters to the FDA in June 2005, twenty-six Senators and seventy-two Congressmen voiced their continued displeasure over the agency's failure to revise the 2003 Guide and subject it to notice and comment procedures. (Davidson Dec. Ex. 6.) The Congressmen noted that

> The Agency's failure to follow through on these commitments has serious consequences. While FDA has had more than ample time to act on its assurances to revise the CPGs, their failed promises to reissue these documents represents *a significant threat to vulnerable patient populations,* both humans and animals, served by compounding pharmacies.[51] Patients are continually threatened with ***1230** not being able to receive crucial, life-giving medications only available from compounding pharmacies. In addition, *pharmacists are being forced to operate under flawed policy, potentially jeopardizing their livelihood and reputation in order to meet patients' essential medication needs.* Further, the FDA has substantially increased inspection and enforcement activities against compounding pharmacies in the last year, premised on the very documents that the agency acknowledges as flawed.

(*Id.*) (Letter from Congressmen Charles Bass and Mike Ross to Dr. Lester M. Crawford, Acting Commissioner, U.S. Food and Drug Administration (June 29, 2005) (emphasis added)).

The lawmakers requested that the FDA "undertake an immediate review of the reasons behind these delays and take the steps necessary to issue proposed CPGs for public review and comment." (*Id.*) However, almost five years later, when FDA filed this enforcement action, and even to date, FDA has not issued the revised guidance it promised in 2004.[52]

6. Medical Center

In 2006, a group of state-licensed compounding pharmacies that specialized in compounding prescription drugs for humans and non-food animals grew weary of waiting for the FDA's promised revisions and brought suit challenging the agency's new assertions of authority as memorialized in the 2002 and 2003 Guides. *Med. Ctr. Pharm. v. Gonzales,* 451 F.Supp.2d 854 (W.D.Tex.2006).[53] The pharmacies sought broad-based injunctive relief, including: (i) a declaration that drugs compounded by licensed pharmacists were not "new drugs" or "new animal drugs" *per se* under the FDCA; (ii) a declaration that the FDA did not have the authority to declare compounding from bulk ingredients for non-food animals illegal; and (iii) an injunction to prevent the FDA from enforcing the 2003 Guide "which unilaterally declares that compounding from bulk ingredients for non-food animals is illegal." ***1231** *Id.* at 856–57. After reviewing § 321(p)(1) and § 321(v)(1), the district court noted "the new drug definitions might seem to indicate that compound drugs fall within their provisions." *Id.* at 859. However, the court ultimately found that *Western States,* FDAMA,[54] and the legislative history of the FDCA compelled the conclusion that "compound drugs are implicitly exempt from the [FDCA's] new drug definitions." *Id.* The court then used this implied exemption to conclude, *inter alia,* that: (i) compounding medications for non food-producing animals from bulk drugs was permissible because the resulting medications were not "new drugs," rendering inapplicable the FDCA's unsafe, misbranding and adulteration provisions; and (ii) the FDA could no longer enforce the 2003 Guide to the extent that it conflicted with the court's analysis of the FDCA. *Id.* at 867–69.

On appeal, the FDA challenged the district court's holdings that compounded drugs were "uniformly exempt" from the FDCA's "new drug" definitions, and that "drugs compounded from bulk ingredients for non-food animals do not violate the FDCA's unsafe, adulteration, or misbranding requirements." *Med. Ctr.,* 536 F.3d at 393. The Fifth Circuit, after reviewing the FDCA in light of its legislative history, initially expressed sympathy for the pharmacies' plight:

> Given the apparent ubiquity of pharmacy compounding at the time Congress passed the FDCA [in 1938], it would have been unprecedented for the FDCA to regulate compounded drugs ... [I]t seems unlikely that Congress intended to force compounded drugs to undergo the new drug approval process, a requirement that would have made compounding nearly impossible and thus nonexistent. Construing the "new drug" definition in a way that makes compounding effectively unlawful appears inconsistent with the likely expectation that compounding would and should persist and with other provisions of the FDCA that expressly acknowledge the existence of compounding. [55]

Id. at 398 (other footnotes omitted).

Ultimately, however, the Fifth Circuit agreed with the FDA that compounded drugs are "new drugs" and consequently must satisfy the FDCA's new drug approval requirements. *Id.* at 394. The Court deflected the argument that this construction would eradicate "the universally-appreciated practice of compounding" because it refused to "infer an absurd result from a maximalist interpretation of the FDA's authority where such authority is tempered by enforcement discretion." *Id.* at 398–99. However, the Court conceded that such discretion would provide little reassurance to the pharmacies:

> The Pharmacies may quite understandably find cold comfort in the FDA's promised self-restraint. In light, however, of the agency's statutorily-authorized enforcement discretion *and demonstrated* ***1232** *willingness to accommodate traditional compounding's continued existence,* there is reason to think pharmacies would continue to compound even if compounded drugs were deemed "new drugs." Construing the FDCA to give the FDA authority over compounding would thus not necessarily "lead to a result so bizarre that Congress could not have intended it."
>
> *Nonetheless, it remains at least questionable that Congress would have intended such a large expansion of the FDA's regulatory authority. And it remains no small burden for compounding pharmacists, as they put it, to "live in sin"—their livelihood having no greater assurance than the FDA's good graces.*

Id. at 399–400 (emphasis added and citation omitted).

Despite these misgivings, the Fifth Circuit found that Congress' enactment of FDAMA made a "difficult case ... easy" because the amendment provided a "safe harbor" for compounding under certain conditions. *Id.* at 400, 405. When construing the statute in light of its amendment, the Court concluded that compounded drugs could not be "implicitly exempted" from the FDCA, as the district court had concluded, because "reading the 'new drug' definition implicitly to exclude compounded drugs would make [FDAMA]'s explicit, conditional exceptions superfluous." *Id.* at 405–06.

At the end of its lengthy opinion, the Court very briefly considered the district court's conclusion that "drug products compounded in bulk by pharmacists and veterinarians are not 'new animal drugs' and therefore are not 'adulterated,' 'unsafe,' or 'misbranded.' " *Id.* at 406–08. The Fifth Circuit declared AMDUCA a "similar amendment" to FDAMA, and thus concluded that although the amendments contain different provisions, [56] "AMDUCA's effect on construction of the 'new animal drug' definition is much the same as FDAMA's effect on construction of the 'new [human] drug' definition. AMDUCA suggests that the FDCA's use of the term 'new animal drug' includes compounded drugs." *Id.* at 407–08 (alteration in original). The Court explained this conclusion by finding that:

> paragraph (4) [of AMDUCA] establishes that if a new animal drug is approved for one animal use, it can be used for a different unapproved use (i.e., compounded), [57] and paragraph (5) provides that if a new drug is approved for human use, it can be used for a different unapproved animal use (i.e., compounded). [58] In both cases, the drug must be used pursuant to the order of a licensed veterinarian and is subject to the FDA's discretionary finding that it poses a risk to public health.

***1233** *Id.* at 408. As a result, the Court held—citing *Algon* and *9/1 Kg. Containers* as additional support—"that compounded drugs are 'new animal drugs' " under the FDCA, "[a]nd unless the compounded drugs are exempt under the FDCA's AMDUCA provisions, § 360b(a)(4) and (5), compounded animal drugs are subject to FDCA's unsafe, adulteration, and misbranding requirements. As with human drugs, the FDCA *contains no blanket 'implicit exemption'* for animal drugs produced by compounding." *Id.* at 408 (emphasis added).

Now, for the first time, the FDA has brought an enforcement action under the FDCA seeking to enjoin a pharmacist from compounding veterinarian-prescribed medications from bulk.

IV. The Court's Decision

A. Introduction

The FDA says this is a simple case: the literal, plain language of the original FDCA, enacted in 1938, gives it the enforcement authority to prevent pharmacists from bulk compounding medications for non food-producing animals. Thus, the FDA asserts that it is authorized to enjoin a licensed pharmacist's state-authorized practice of compounding animal drugs from bulk substances, even where a *single* medication is compounded for an individual non food-producing animal pursuant to a valid veterinary prescription. Essentially, the FDA contends that this traditional compounding practice implicates the same concerns under the FDCA as the mass-production, mass-marketing, and mass-distribution of unapproved animal drugs by an unlicensed manufacturer. [59]

Although the FDA's complaint and declarations contain allegations that Franck's has engaged in conduct indicative of a "manufacturer" of drugs, such as compounding commercially available drugs or compounding drugs in advance of a valid prescription, it has provided no factual support for such claims and ultimately does not rely on them to maintain this action. Further, despite the FDA's allusions to Franck's "large" and "interstate" operation, it has not sought to prove a statutory violation based on the size or breadth of Franck's operation. Nor does the FDA contend that Franck's has compounded from bulk substances so as to produce animal drugs which are actually unsafe for animal consumption or are not efficacious. *See* Doc. 47 at 37–38. Finally, though the FDA references the deaths of the Venezuelan polo horses, that tragic event was unrelated to the bulk compounding that the FDA targets in this suit. Thus, each of these matters proved to be irrelevant. Given the undisputed record in this case and the FDA's broad view of its authority under the FDCA, this enforcement action could just as easily have been brought against a state-licensed "Mom–and–Pop" pharmacy for filling, through bulk compounding, one veterinary prescription for one horse.

Narrowing the inquiry even further, the FDA contends that it needs no more than the plain language of the 1938 FDCA to enjoin Franck's bulk compounding, a position it asserts has been confirmed by three courts of appeal (the Seventh, Third, and Fifth Circuits in *9/1 Kg. Containers,* ***1234** *Algon,* and *Medical Center,* respectively). The FDA expressly disclaims reliance upon any other legal source, including AMDUCA, (*see* Doc. 54 at 7 ("AMDUCA does not encompass compounding from bulk drugs")); (Doc. 47 at 20 ("AMDUCA doesn't touch what we have here in this case")); FDAMA, (*id.* at 42 ("neither [FDAMA nor AMDUCA] are the subject of this suit")); any FDA regulation; [60] or the 2003 Guide, which it concedes does not have the force of law, (Doc. 54 at 30 (the 2003 Guide "is nothing more than an expression of a non-binding policy on enforcement discretion")). Thus, reduced to its essence, the parties and the Court are joined on the central issue: whether the FDCA, as originally enacted in 1938, provides the FDA with statutory authority to enjoin Franck's from engaging in traditional compounding of animal drugs from bulk.

Franck's says that Congress, in passing the FDCA, never intended to allow the FDA to prohibit the long-standing and widespread practice of bulk compounding when done by a state-licensed, state-regulated pharmacist, acting on an individual prescription written by a veterinarian for a non food-producing animal. In the alternative, Franck's contends that the FDA has failed to properly exercise this authority by failing to promulgate regulations through notice and comment rule-making before commencing this enforcement action. [61]

The FDA acknowledges that, for over a half-century after enactment of the FDCA, it did not assert authority to regulate traditional pharmacy compounding. Despite this, the agency's position is that the FDCA has always provided the FDA with authority to bring enforcement actions against pharmacists who compound animal drugs,

and that its failure to do so in the past was merely the exercise of prosecutorial discretion. The FDA further asserts that it need not undertake rule-making before seeking to regulate in this area because its authority is supported by the plain language of the FDCA. The FDA thus concludes that, once it has shown a violation of the statute (i.e., that a "new animal drug" has been distributed without an approval or exemption in place), it enjoys unfettered enforcement discretion.

B. Discussion

[4] "Because this case involves an administrative agency's construction of a statute it administers, [this Court's] analysis is governed by *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.,* 467 U.S. 837, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984)." *FDA v. Brown & Williamson Tobacco Corp.,* 529 U.S. 120, 132, 120 S.Ct. 1291, 146 L.Ed.2d 121 (2000). Under *Chevron*' s two-step approach, a reviewing court must first ask "whether Congress has directly spoken to the precise question at issue[, and i]f the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron,* 467 U.S. at 842–43, 843 n. 9, 104 S.Ct. 2778 ("If a ***1235** court, employing traditional tools of statutory construction, ascertains that Congress had an intention on the precise question at issue, that intention is the law ...."). Second, if the Court finds that "the statute is silent or ambiguous with respect to the specific issue," the Court will defer to the agency's interpretation if it is "based on a permissible construction of the statute." *Chevron,* 467 U.S. at 843, 104 S.Ct. 2778; *see also Gonzales v. Oregon,* 546 U.S. 243, 255, 126 S.Ct. 904, 163 L.Ed.2d 748 (2006) ("An [agency's] interpretation of an ambiguous statute may ... receive substantial deference") (citing *Chevron,* 467 U.S. at 842–45, 104 S.Ct. 2778).

In applying this two-step analysis, the Supreme Court found in *Chevron* that " '[t]he power of an administrative agency to administer a congressionally created ... program necessarily requires the formulation of policy and the making of rules to fill any gap left, implicitly or explicitly, by Congress.' " *Chevron,* 467 U.S. at 843, 104 S.Ct. 2778 (quoting *Morton v. Ruiz,* 415 U.S. 199, 231, 94 S.Ct. 1055, 39 L.Ed.2d 270 (1974)). Thus, "a court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency." *Id.* at 844, 104 S.Ct. 2778. However, the Court also recognized the judiciary's role as "the final authority on issues of statutory construction." *Id.* at 843 n. 9, 104 S.Ct. 2778. As a result, "a reviewing court 'must reject administrative constructions ... that are inconsistent with the statutory mandate or that frustrate the policy that Congress sought to implement.' " *Sierra Club v. Johnson,* 541 F.3d 1257, 1265 (11th Cir.2008) (quoting *Sec. Indus. Ass'n v. Bd. of Governors of Fed. Reserve Sys.,* 468 U.S. 137, 143, 104 S.Ct. 2979, 82 L.Ed.2d 107 (1984)). Further, "deference to the agency's interpretation under *Chevron* is warranted only where 'Congress has left a gap for the agency to fill pursuant to an express or implied delegation of authority to the agency.' " *Am. Bar Ass'n v. F.T.C.,* 430 F.3d 457, 468 (D.C.Cir.2005) ("*ABA I* ") (quoting *Ry. Labor Exec. Ass'n v. Nat'l Mediation Bd.,* 29 F.3d 655, 671 (D.C.Cir.1994) (en banc)). Put differently, "the existence of [statutory] ambiguity is not enough *per se* to warrant deference to the agency's interpretation. The ambiguity must be such as to make it appear that Congress either explicitly or implicitly delegated authority to cure that ambiguity." *Id.* at 469.

1. The FDCA's Language and the New Animal Drug Approval Process

"We begin, as courts always should in matters involving statutory interpretation, with the statutory language." *Durr v. Shinseki,* 638 F.3d 1342, 1344 (11th Cir.2011). The FDCA broadly defines "drug" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." 21 U.S.C. § 321(g)(1)(B). The term "new animal drug" is also broadly defined as

> *any* drug intended for use for animals other than man ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective [62] for use under the conditions ***1236** prescribed, recommended, or suggested in the labeling thereof.

Id. § 321(v)(1) (emphasis added). This definition provides no general exception for drugs created by compounding, nor a specific exemption for compounding by pharmacists. As the Fifth Circuit noted in *Medical Center,*

> [T]he language of the FDCA's "new drug" [63] definition is both plain and expansive. A "new drug" is

> "any drug" the "composition of which" has not already been approved for use in accordance with its labeling. Compounded drugs are, after all, drugs. If a compounder changes the composition of an approved drug—by mixing or combining an approved drug with something else to create a different substance or by creating special dosage or delivery forms of an approved drug inconsistent with a drug's labeling—the composition of the individualized concoction created by a compounding pharmacist will not have been previously approved for use. The resulting substance is therefore a "new drug."
>
> Belying the Pharmacies' argument that compounded drugs are not "new drugs" by virtue of their creation by licensed pharmacists, *the definition of "new drug" focuses on the drug's composition and use rather than on the process by which it was created.* Under the plain language of § 321(p)(1) [and § 321(v)(1)], it does not matter that the substance has been created through compounding rather than manufacturing—whether it be through rigorous research and development by a pharmaceutical company, through individualized compounding by a pharmacist or through cut-rate production by a rogue manufacturer. Regardless of how and by whom it was created, "any" such substance constitutes a "new drug" within the meaning of § 321(p)(1) [and § 321(v)(1)].
>
> *Med. Ctr.,* 536 F.3d at 395 (emphasis added, footnote omitted).

Before introducing or distributing a "new animal drug," a person must file an application that includes a number of detailed findings. 21 U.S.C. § 360b(b)(1). These include: full reports of investigations demonstrating that the drug is safe and effective for use; a list of the components of the drug; a statement of the drug's composition; a description of the manufacturing, processing, and packaging of the drug; samples of the drug; proposed labeling for the drug; methods for determining its effect on food, if any; and, proposed tolerances or withdrawal periods, if any. *Id.* A new animal drug is deemed "unsafe" under the FDCA unless the drug, its labeling, and its intended use conform to the FDA-approved application, a conditional approval, or an index listing for use in a minor species. *Id.* § 360b(a)(1). A drug is deemed "adulterated" if "it is a new animal drug which is unsafe within the meaning of [21 U.S.C. § 360b]." *Id.* § 351(a)(5). Lastly, the FDCA requires any new drug to be labeled with adequate information about its contents, intended uses, and effects; drugs that fail to meet this requirement are "misbranded." *See id.* § 352. The FDCA prohibits the production, sale, and distribution of adulterated ***1237** or misbranded drugs; *see* 21 U.S.C. § 331(a)-(c), (k); and authorizes the FDA to enforce its approval provisions utilizing both criminal and civil penalties. *See* 21 U.S.C. §§ 332 (injunction proceedings), 333 (criminal penalties), 334 (seizure), 335(b) (civil penalties).

Thus, read literally, the type of bulk compounding performed by Franck's (and hundreds of other pharmacists across the country on a daily basis) creates "new animal drugs" within the FDCA's broad definition of that term. According to the FDA, the Court's inquiry ends here. Franck's compounds animal medications from bulk substances (and in so doing implicates the interstate nexus); those medications are "new animal drugs" within the plain language of the FDCA; no statutory exceptions apply which would exempt compounded animal drugs from the FDCA's misbranding or adulteration provisions; the FDA has authority to enforce the new drug approval scheme; and it has chosen to do so here. Thus, FDA urges this Court to "follow the holdings of the Third, Fifth, and Seventh Circuits [in *Algon, Medical Center,* and *9/1 Kg. Containers*] that compounded animal drugs are 'new animal drugs' within the meaning of the FDCA and decline [Franck's'] invitation to re-litigate the issue." Doc. 60 at 7.

2. Algon, 9/1 Kg. Containers, and Medical Center

Algon and *9/1 Kg. Containers* each addressed the enforceability of an FDA regulation that exempted bulk drug sales from the FDCA's labeling requirements but limited the exemption to holders of new drug approval applications, thereby excluding veterinarians from the exemption. *See Algon,* 879 F.2d at 1156 (quoting 21 C.F.R. § 201.122); *9/1 Kg. Containers,* 854 F.2d at 175 (same). In so doing, the Third and Seventh Circuits analyzed the FDCA and noted that "[t]he statutory definition of a 'new drug' ... does not exempt drugs that are compounded by veterinarians." *Algon,* 879 F.2d at 1158; *see also 9/1 Kg. Containers,* 854 F.2d at 175, 179. As a result, the courts concluded that "[t]he effect of § 352(f) [the FDCA's misbranding provision] and § 201.122 [the bulk drug exemption] is that ingredients that can be used to produce 'new' drugs may be sold only to firms that hold approved (or have filed) new animal drug applications." *Algon,* 879 F.2d at 1157–58 (quoting *9/1 Kg. Containers,* 854 F.2d at 178).

There is no doubt that *Algon* and *9/1 Kg. Containers* favor a broad reading of the FDA's authority under the FDCA. *See 9/1 Kg. Containers,* 854 F.2d at 176 ("Courts defer to the FDA when it construes its governing statutes"). However, though *Algon* and *9/1 Kg. Containers* certainly have implications for this case, they are not on all fours either factually or procedurally. Both cases were enforcement actions against *suppliers* to prohibit them from supplying unapproved bulk ingredients to *veterinarians* for use in compounding.[64] Neither case mentioned pharmacists or the practice of pharmacy.[65] ***1238** Thus, neither court had occasion to consider the FDA's asserted authority to enjoin the practice of traditional pharmacy compounding.[66] This case presents that question, a different (though related) one from that faced in *Algon* and *9/1 Kg. Containers. Id.*[67]

[5] **[6]** **[7]** *Algon* and *9/1 Kg. Containers* also predate a number of important legal developments relating to both the FDA's regulation of compounding and the *Chevron* doctrine. Both were decided before the Supreme Court in *Brown & Williamson* recognized that in certain circumstances, a literal reading of a broadly drawn public health statute (specifically, the FDCA) should be rejected when it encompasses conduct which exceeds the original congressional intent. *See infra,* Sec. IV(B)(3)(a). Moreover, two years after deciding *Brown & Williamson,* the Supreme Court in *Western States* expressly acknowledged the historical importance of traditional pharmacy compounding, and openly questioned whether Congress could have intended to subject compounded drugs to the FDCA's new drug approval process. *See W. States,* 535 U.S. at 369–70, 122 S.Ct. 1497. To answer this question, Franck's urges application of several canons of statutory construction (specifically, the "elephant-in-mouseholes doctrine,"[68] the "plain statement rule,"[69] and the "rule of lenity"[70]), none of which were argued or applied in the cases before the Third and Seventh Circuits (indeed, the elephant-in-mouseholes doctrine did not yet exist).

Medical Center (discussed in detail *supra,* Sec. III(B)(6)), though more similar to this case, is also different in important ways. First, *Medical Center* was not an FDA enforcement proceeding aimed at a specific target. Rather, the plaintiff pharmacies ***1239** in that case sought broad-based prospective declaratory relief, i.e., to be excluded *entirely* from the FDCA's new drug approval regime, a position that the district court vindicated by holding that *all* compounded drugs enjoyed an "implicit exemption" from the FDCA. It was upon this premise that the district court based each of its subsequent findings—including the conclusion that pharmacy compounding of animal drugs from bulk did not fall within the FDA's enforcement authority.[71] *See Med. Ctr.,* 536 F.3d at 392 n. 20 (explaining that the district court "framed the Pharmacies' requested declaratory judgment as a 'declaration that drugs compounded by licensed pharmacists are not 'new drugs' or 'new animal drugs' *per se*' ").[72]

The pharmacies' position (and the district court's holding) was simply untenable because, as Franck's concedes, the FDA *does* have the authority to prohibit pharmacists from manufacturing under the guise of compounding. *Cf. Med. Ctr.,* 536 F.3d at 399 ("Construing the FDCA to give the FDA authority *over compounding* would thus not necessarily 'lead to a result so bizarre that Congress could not have intended it.' ") (emphasis added and citation omitted); *In re Wedgewood Vill. Pharmacy,* 270 F.Supp.2d 525, 549 (D.N.J.2003) ("Congress intended that the FDCA, both in its original form and as amended, allow the FDA broad enforcement powers to fulfill its mandate that it protect the public from unsafe medication"). Thus, the Fifth Circuit was understandably reluctant to issue a blanket declaration that the FDA could not regulate pharmacists who compromised the FDCA's new drug approval scheme, especially in light of the agency's "promised self-restraint" in bringing enforcement proceedings and its "demonstrated willingness to accommodate traditional compounding's continued existence." *Med. Ctr.,* 536 F.3d at 399. The Court therefore declined to "*infer an absurd result from a maximalist interpretation* of the FDA's authority where such authority is tempered by enforcement discretion." *Id.* (emphasis added).

The Fifth Circuit was able to reject a "maximalist" interpretation of the FDA's authority because the FDA was not advancing such a position. Here, however, the FDA is taking the "maximalist" position that any pharmacy compounding of animal drugs from bulk substances pursuant to a valid veterinary prescription —which, according to the undisputed record evidence, would qualify as "traditional compounding"[73] —is *per se* unlawful under the FDCA.[74] Thus, the Fifth Circuit's

faith that the FDA would not seek to enforce a "maximalist" interpretation of its authority turned out to be misplaced.

There is an additional problem with the Fifth Circuit's disposition when overlaid upon this case. Not only did the Court in *Medical Center* presume that the FDA would continue to demonstrate its historical willingness to accommodate traditional compounding, but it also presumed that the FDA drew no distinction between human ***1240** and animal compounding, even though the manifest differences in the 2002 and 2003 Guides belie such a presumption. Here, the FDA is not only asserting its authority to regulate traditional compounding, but is drawing an enforcement line between human and animal drugs. Although Franck's compounds medications for both humans and animals, the FDA is not seeking to enjoin Franck's' human compounding business. Rather, the FDA (despite its statement in the 2002 Guide that "all of FDAMA is now invalid") takes the position in this litigation that the FDCA is "more constrictive" with regard to non food-producing animal drugs than it is for human drugs.[75] Though the FDA concedes that this is an unfortunate position to argue from, it contends that interpreting the FDCA—a prophylactic statute designed to protect the public health—in a manner that is less protective of humans than of non food-producing animals "is simply a matter of applying the statutes as written." Doc. 54 at 16. While this statutory inconsistency should theoretically have been before the Court in *Medical Center,* which passed on the question of both human and animal compounding, the Fifth Circuit did not address it.[76]

[8] And lastly, in analyzing the FDA's interpretation of its authority under the FDCA to regulate compounding, each of the Third, Fifth, and Seventh Circuits afforded *Chevron*-level deference to the agency. In *Algon* and *9/1 Kg. Containers,* this was appropriate because both cases involved a challenge to an FDA regulation promulgated pursuant to notice-and-comment rule-making. The courts thus showed substantial deference to the FDA's construction of the FDCA and its own regulations[77] and placed the burden on the suppliers to show that the "FDA's views about the needs of public health [we]re arbitrary and capricious." *9/1 Kg. Containers,* 854 F.2d at 176; *Algon,* 879 F.2d at 1159. This, as the Seventh Circuit noted, was a "doubly-uphill battle." *9/1 Kg. Containers,* 854 F.2d at 176.

Likewise, because the Fifth Circuit concluded on the basis of FDAMA and AMDUCA that the plain language of the FDCA encompassed compounded drugs, it deferred to the FDA's enforcement discretion in regulating pharmacy compounding:

> When it comes to the slippery task of distinguishing true compounding from disguised manufacturing, we should question our own capacity, as a court, to ***1241** make that distinction in future cases. In exercising its discretion, the FDA relies on numerous factors and considerations to determine whether a pharmacist is engaged in compounding as distinguished from manufacturing. With no guidance from the statutory text, we doubt we could do any better, and we are wary of trading the FDA's discretion for our own.

Med. Ctr., 536 F.3d at 399 (footnote omitted).

For reasons explained more fully *infra, Chevron* deference is not appropriate in this case, which provides yet another basis for distinguishing *Algon, 9/1 Kg. Containers,* and *Medical Center.*

3. Chevron Step One: Whether Congress Intended to Grant the FDA Authority to Regulate Traditional Compounding

[9] The FDA argues that, even if *Algon, 9/1 Kg. Containers,* and *Medical Center* are distinguishable, this Court must find that the plain terms of the FDCA encompass compounded drugs because the FDCA grants the FDA "broad authority" to regulate drugs "to ensure public health and safety." *Nutritional Health Alliance v. FDA,* 318 F.3d 92, 97–98 (2d Cir.2003). As the FDA notes, the primary purpose of the FDCA is to protect and safeguard consumers from dangerous products. *United States v. Sullivan,* 332 U.S. 689, 696, 68 S.Ct. 331, 92 L.Ed. 297 (1948); *see also Brown & Williamson,* 529 U.S. at 133, 120 S.Ct. 1291 (a "core objective" of the FDCA is to "ensure that any product regulated by the FDA is 'safe'

and 'effective' for its intended use"). To effectuate that purpose, the Supreme Court has instructed that "Congress fully intended that the [FDCA]'s coverage be as broad as its literal language indicates.... [R]emedial legislation such as the [FDCA] is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health." *United States v. Article of Drug ... Bacto–Unidisk,* 394 U.S. 784, 798, 89 S.Ct. 1410, 22 L.Ed.2d 726 (1969). Thus, the FDA simply asks that this Court enjoin Franck's from distributing animal medications compounded from bulk substances because the FDCA statutorily defines those drugs as unsafe, adulterated, and misbranded.

Franck's concedes that the literal language of the "new animal drug" provision read without any other context is sufficiently capacious to encompass pharmacists and compounding, but argues that further inquiry is necessary to determine whether such an outcome was intended by Congress in 1938. Franck's contends that Congress never meant the FDCA to reach so broadly as to allow the FDA to enjoin the long-standing practice of a state-licensed pharmacist using traditional bulk compounding to fill a veterinarian's prescription for a non food-producing animal. Stated differently, Franck's position is not that Congress left open an implied exception for traditional pharmacy compounding; rather, Franck's argues that Congress never intended to regulate the practice in the first place. *See ABA I,* 430 F.3d at 469. Franck's therefore urges this Court to consider the FDCA's structure and legislative history through the lens of several canons of statutory construction so as to place the FDCA's treatment of traditional pharmacy compounding in its proper context.

a. Elephants-in-mouseholes doctrine

[10] Franck's finds support in *Brown & Williamson, ABA I,* and *Gonzales.* In *Brown & Williamson,* the FDA asserted jurisdiction to regulate tobacco products based on its conclusions that nicotine was a "drug" and that cigarettes and smokeless tobacco were "drug delivery devices" under the FDCA. ***1242** 529 U.S. at 131, 120 S.Ct. 1291. While tobacco products appeared at first blush to be encompassed by the FDCA's literal definitions, which might have rendered the statute unambiguous on the question, the Court cautioned that " '[a]mbiguity is a creature not of definitional possibilities but of statutory context.' " *Id.* at 132–33, 120 S.Ct. 1291 (quoting *Brown v. Gardner,* 513 U.S. 115, 118, 115 S.Ct. 552, 130 L.Ed.2d 462 (1994)). As such, the Court stated that "[i]n determining whether Congress has specifically addressed the question at issue, a reviewing court should not confine itself to examining a particular statutory provision in isolation. The meaning—or ambiguity—of certain words or phrases may only become evident when placed in context." *Id.* at 132, 120 S.Ct. 1291. After interpreting the FDCA "as a symmetrical and coherent regulatory regime," the Court declared that "Congress could not have intended to delegate a decision of such economic and political significance to an agency in so cryptic a fashion." *Id.* at 133, 120 S.Ct. 1291 (citation omitted), 160.[78] As a result, and after consideration of subsequent legislation addressing the issue, the Court found that "the FDA's claim to jurisdiction contravenes the clear intent of Congress." *Id.* at 132, 120 S.Ct. 1291.

Likewise, in *ABA I,* the FTC asserted authority to regulate certain attorneys as "financial institution[s]" under the privacy provisions of the Gramm–Leach–Bliley Act ("GLBA"). 430 F.3d at 465–66. The D.C. Circuit noted that neither the statute nor the FTC's regulations described the regulatory scheme as governing the practice of law, and that the word "attorney" did not appear in the GLBA in such a context so as to include attorneys within the definition of "financial institution." *Id.* at 466. However, because the GLBA defined "financial institution" "quite broadly," under the literal language of the statute, real estate and tax attorneys were potentially implicated through a weave of incorporated statutes and regulations. *Id.* at 467 (citation omitted).

The Court declared that:

> [t]he statute certainly does not so plainly grant the Commission the authority to regulate attorneys engaged in the practice of law as to entitle the Commission to what is called a "*Chevron* One" disposition. That is, rather simply we cannot hold that Congress has directly and plainly granted the Commission the authority to regulate practicing attorneys as the Commission attempts. Indeed, such professionals are subject to regulation under the words of the statute only if they are "institutions" and if they are "engaged in the business of financial activity." It is not plain at all to us that Congress has entered such a direct regulatory command by plain language of a statute, a lengthy statute incorporated by reference, and an even more lengthy and detailed regulation

> incorporated by reference in the second statute, none of which ever mentioned attorneys engaged in the practice of law. Therefore, if the Commission is to prevail, it must do so under a deferential standard of review. That is, to uphold the Commission's regulatory decision, we must conclude first that the words of the statute are ambiguous in such a way as to make the Commission's decision worthy of deference under the second step of *Chevron.*

Id. at 467–68. The Court reviewed the regulatory scheme in light of the traditional state regulation of attorneys, and noted that the statutory language, while potentially broad or ambiguous enough to bear FTC's interpretation, made for an "exceptionally ***1243** poor fit with the FTC's apparent decision that Congress, after centuries of not doing so, has suddenly decided to regulate the practice of law." *Id.* at 470. Applying the elephant-in-mouseholes doctrine, the Court concluded that Congress did not "intend[ ] to undertake the regulation of the profession of law—a profession never before regulated by 'federal functional regulators'—and never mentioned in the statute." *Id.* at 469.

And most recently, the Supreme Court in *Gonzales* considered "whether the Controlled Substances Act allows the United States Attorney General to prohibit doctors from prescribing regulated drugs for use in physician-assisted suicide, notwithstanding a state law permitting the procedure." 546 U.S. at 248–49, 126 S.Ct. 904. After a lengthy review of the Attorney General's delegated authority and the structure of the CSA, the Court declared "[t]he idea that Congress gave the Attorney General such broad and unusual authority through an implicit delegation in the CSA's registration provision is not sustainable." *Id.* at 267, 126 S.Ct. 904 (citing *American Trucking,* 531 U.S. at 468, 121 S.Ct. 903; *Brown & Williamson,* 529 U.S. at 160, 120 S.Ct. 1291). Applying the appropriate level of deference due to the Attorney General's position, the Court found the Attorney General's statutory interpretation to be unpersuasive. *Id.* at 268–69, 126 S.Ct. 904. [79]

The elephant-in-mouseholes doctrine is equally applicable here: it is not at all clear that Congress meant to hide the elephant of the FDA's regulation of traditional pharmacy compounding in the mousehole of the FDCA's new drug approval process. Every court that has addressed the issue —no matter the context—has recognized that the FDA new drug approval process is an "especially poor fit" for regulating traditional pharmacy compounding, one that would potentially eradicate traditional compounding despite the recognized importance, historical acceptance, and decades-long state regulation of the practice. *See, e.g., W. States,* 535 U.S. at 369–70, 122 S.Ct. 1497 ("[I]t would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs"); *Med. Ctr.,* 536 F.3d at 398 ("[I]t seems unlikely that Congress intended to force compounded drugs to undergo the new drug approval process, a requirement that would have made compounding nearly impossible and thus nonexistent"); *see also Algon,* 879 F.2d at 1161 (noting the argument that "limiting drugs that veterinarians can compound to those lawfully obtainable [at the time, approved animal drugs] means for all practical purposes that veterinarians will be unable to compound"); *9/1 Kg. Containers,* 854 F.2d at 177 ("The testing required to obtain a new animal drug approval is costly and extended ... Testing must isolate the effects of the drug in question from all other environmental influences, then follow the animals for years (even generations of animals) to identify the consequences. This requires data from large populations of animals and the application of powerful statistical techniques. No solitary medical professional can carry out this program of knowledge acquisition for even one drug, let alone for the bevy of drugs a veterinarian may choose to compound." ***1244**). Likewise, despite the literal language of the statute, this Court cannot find that Congress has "directly and plainly" said that traditional pharmacy compounding of animal drugs must meet the requirements of the FDCA's new drug approval provisions. *See ABA I,* 430 F.3d at 467; *American Bar Ass'n v. F.T.C.,* 671 F.Supp.2d 64, 73 (D.D.C.2009) ("*ABA II* "), *vacated on mootness grounds, American Bar Ass'n v. F.T.C.,* 636 F.3d 641, 644 (D.C.Cir.2011).

[11] Where Congress has not entered a direct regulatory command by the plain language of the statute, further review is warranted to determine whether the statute is "ambiguous in such a way as to make the [agency's] decision worthy of deference under the second step of *Chevron*." *ABA I,* 430 F.3d at 468. The question of

whether such an ambiguity exists "is for the court, and we owe the agency no deference on the existence of ambiguity. Deference to the agency's interpretation under *Chevron* is warranted *only where Congress has left a gap for the agency to fill pursuant to an express or implied delegation of authority to the agency.*" *Id.* at 467 (emphasis added and internal quotation omitted). The Court must therefore proceed with a review of the structure and legislative history of the FDCA, using recognized canons of statutory construction, to determine whether deference to the FDA's statutory construction is appropriate here.

b. Statutory structure, legislative history and the FDCA's purpose

Though nothing in the FDCA or its amendments actually *prohibits* compounding by a state-licensed pharmacist, the FDA posits that an explicit prohibition is not required for the agency to enforce against the practice. Rather, the FDA argues that because the statute includes no *exemption* for state-licensed pharmacists or for compounded medications, traditional pharmacy compounding practices are subject to the same regulatory requirements as new drugs that are manufactured, marketed, and distributed in interstate commerce.[80] The lack of a blanket exemption for pharmacy compounded drugs is at least somewhat instructive because the FDCA does exclude certain "grandfathered" old drugs and investigational drugs from the scope of its "new animal drug" provisions. *See* 21 U.S.C. § 321(v)(1), § 360b(j).

However, "if we were 'to *presume* a delegation of power' from the absence of 'an express *withholding* of such power, agencies would enjoy virtually limitless hegemony.' " *ABA I,* 430 F.3d at 468 (emphases in original) (quoting *Ry. Labor,* 29 F.3d at 671). And while pharmacists do not enjoy a uniform exemption from the FDCA's new drug approval scheme, the 1962 amendments to the FDCA do exempt from certain FDA registration and inspection requirements "pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy" and dispense drugs "upon prescriptions of practitioners" for their patients, "and which do not manufacture ... [or] compound ... drugs ... for sale *other than in the regular course of their business of dispensing or selling drugs.*" *See* 21 U.S.C. § 360(g)(1) (requiring drug manufacturers to register annually with the FDA) (emphasis added); ***1245** *id.* § 374(a)(2)(A) (granting FDA agents right to inspect manufacturing facilities "[f]or purposes of enforcement of this chapter"). Interestingly, these provisions contain the FDCA's only mention of compounding, and arise in a context which expressly distinguishes drug manufacturers from pharmacists engaged in the practice of traditional compounding. The presence of these exemptions could be interpreted as a congressional policy decision to distinguish compounding from manufacturing. In fact, this very interpretation was recognized by the Third and Seventh Circuits in *Algon* and *9/1 Kg. Containers* in the context of veterinarians. *See Algon,* 879 F.2d at 1160 ("Congress *intended to authorize compounding with legally acquired drugs* ... Thus, the medical practitioner exemptions by their terms afford no more than the right to be free from inspection and registration requirements when veterinarians and other practitioners *compound medicine with legally acquired materials* ") (emphasis added); *9/1 Kg. Containers,* 854 F.2d at 177–78 ("The FDA treats § 360(g)(2) as *allowing veterinarians to* 'prepare, propagate, *compound,* or process drugs *from ingredients they lawfully acquire',* and the added words are no more than those implied in every statute") (first emphasis added); *see also U.S. v. Baxter Healthcare Corp.,* 901 F.2d 1401, 1409 (7th Cir.1990) ("Congress *has decided to treat commercial manufacturers of drugs differently from pharmacies and individual physicians* in [certain] contexts [citing the FDCA's exemption of pharmacists and physicians from the registration and inspection requirements in 21 U.S.C. §§ 360(g)(1), (2), 374(a)(1), (2)]. Therefore, *to the extent Congress has addressed the issue, it has decided to focus governmental resources upon the commercial distributors of drugs rather than upon the trained pharmacists and physicians who must reconstitute drugs for patient use on a smaller scale.* One sound argument for this choice is evident: A drug improperly compounded on a large scale will harm more patients than the same compounding mistake made on a smaller scale.") (emphasis added).

The legislative history of the FDCA also supports the view that manufacturers, not compounding pharmacists, were the intended target of the FDCA's new drug approval scheme.[81] Because Congress appeared to be focused on the fact that manufacturing—unlike the practice of pharmacy—was conducted by unlicensed, unregulated nonprofessionals, it seems unlikely that it would have intended to subject ***1246** professionally dispensed drugs to the same regulatory scheme. This distinction is even more compelling when one considers the FDCA

scheme's poor fit with a traditionally compounded animal medication. The FDCA provides that the introduction or delivery for introduction into interstate commerce of any "new animal drug" without FDA approval is unlawful unless an application is filed that includes, among other things, "a full list of the articles used as components of such drug." 21 U.S.C. §§ 360b(a)(1), (b)(1)(B). And it requires "full reports of investigations" as part of the application, *id.* § 360b(b)(1)(A), which the FDA has long interpreted to require that new drugs be subject to extensive testing and well-controlled studies to determine their safety and effectiveness. Given that traditionally compounded medications are prepared for individual animal patients in response to a valid veterinary prescription, meaning each compounded medication has unique components and is ill-suited for "adequate and well-controlled studies," it just does not seem plausible that Congress would have intended to subject pharmacy compounded drugs to the lengthy and expensive new animal drug approval process. *See Med. Ctr.,* 536 F.3d at 398; *W. States,* 535 U.S. at 369–70, 122 S.Ct. 1497. The statutory "fit" is especially poor when compounded medications are the best—and sometimes only—way to treat an animal. *Cf. supra* n. 21 and accompanying text.

However, "statutory prohibitions often go beyond the principal evil to cover reasonably comparable evils, and it is ultimately the provisions of our laws rather than the principal concerns of our legislators by which we are governed." *Oncale v. Sundowner Offshore Servs., Inc.,* 523 U.S. 75, 79, 118 S.Ct. 998, 140 L.Ed.2d 201 (1998). While the FDCA might not have been focused on pharmacists behaving badly, it was without question enacted to protect the public from the distribution of unapproved drugs which have been mass-produced without any assurances of safety or quality control. To the extent that a pharmacist's bulk compounding activity moves beyond the bounds of traditional compounding and begins to approximate the "manufacturing" of unapproved drugs, there seems little question that this activity is squarely within the crosshairs of the FDCA. *Cf. W. States,* 535 U.S. at 361, 122 S.Ct. 1497 ("The Federal Food, Drug, and Cosmetic Act of 1938 ... regulates drug *manufacturing,* marketing, and distribution") (emphasis added).

Thus, on the one hand, legitimate state-licensed pharmacists have long held the right to bulk compound drugs to fill individual prescriptions, and the desirability and acceptance of that practice has been recognized in various ways by Congress and the FDA. On the other, the FDA needs to be able to enforce against manufacturers masquerading as pharmacy compounders. And the new drug approval process is a poor method for drawing a line between these two interests *precisely* because it fails to allow for the continuance of state-authorized, traditional compounding. This tension was duly noted by the Supreme Court in *Western States:*

> Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. *The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs ... Given this, the Government needs to be able to draw a line between small-scale compounding and large-scale drug manufacturing.* That line must distinguish compounded drugs produced on such a small scale ***1247** that they could not undergo safety and efficacy testing from drugs produced and sold on a large enough scale that they could undergo such testing and therefore must do so.

W. States, 535 U.S. at 369–70, 122 S.Ct. 1497 (emphasis added).

What the Supreme Court recognized is that Congress delegated to the FDA the authority to *draw a line* distinguishing between compounded drugs that *must* undergo the new drug approval process because they bear the attributes of having been "manufactured" and "compounded drugs *created to meet the unique needs of individual patients,*" because it "would not make sense" for the latter "to undergo the testing required for the new drug approval process." *Id.* at 369, 122 S.Ct. 1497 (emphasis added); *see also Med. Ctr.,* 536 F.3d at 398. At the time of the Supreme Court's decision in *Western*

States, the government seemed to understand and support this distinction:

> While it praises the FDCA's new drug approval process, the Government also acknowledges that 'because obtaining FDA approval for a new drug is a costly process, requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient *would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment.*'

W. States, 535 U.S. at 369, 122 S.Ct. 1497 (quoting the Government's brief) (emphasis added).

Following this logic, the States, including Florida, expressly distinguish the practice of traditional pharmacy compounding from manufacturing. The Florida Drug and Cosmetic Act, Fla. Stat. §§ 499.001 *et seq.,* which was enacted to "provide uniform legislation *to be administered so far as practicable in conformity with the provisions of, and regulations issued under the authority of, the Federal Food, Drug, and Cosmetic Act,*" *id.* § 499.002(b) (emphasis added), defines "manufacture" as "the preparation, deriving, *compounding,* propagation, producing, or fabrication of any drug, device, or cosmetic," *id.* § 499.003(30) (emphasis added), and "manufacturer" as, *inter alia,* "[a] person who prepares, derives, *manufactures,* or produces a drug, device or cosmetic," *id.* § 499.003(31) (emphasis added). However, the term manufacturer "*does not include a pharmacy that is operating in compliance with pharmacy practice standards as defined in [the Florida Pharmacy Act] and rules adopted [there]under.*" *Id.* § 499.003(31) (emphasis added). And, as mentioned *supra,* those standards and rules expressly provide for compounding from bulk substances. [82]

The Florida statutory scheme recognizes a critical difference between traditional ***1248** pharmacy compounding and manufacturing: the existence of a pharmacist-prescriber-patient relationship that controls the preparation of the compounded drug product. [83] Traditionally compounded drugs are not for resale, but rather are responsive to the patient's immediate needs as diagnosed by the patient's licensed healthcare professional, i.e., a veterinarian. [84] Moreover, unlike manufacturers, compounding pharmacists are licensed professionals who must operate in conformance with applicable state laws that regulate the practice of pharmacy.

Though it certainly has the statutory authority to do so, the FDA has chosen not to draw the line between manufacturing and traditional compounding with formal regulations. Nor has it sought to distinguish traditional pharmacy compounding from pharmacists who are manufacturing under the guise of compounding. [85] Rather, beginning with the 1992 Guide, it has utilized Compliance Policy Guides to disseminate its policy determinations vis-a-vis the acceptability of compounding animal and human drugs. Along the way those non-binding guidance documents have made clear that "traditional pharmacy compounding" [86] was not the subject of the FDA's guidance. In addition, the agency has continued to recognize that because of an "insufficient variety of approved medications," (*see* Flynn Dec. ¶ 26), certain compounded medications are medically necessary for the treatment of animals. [87] Accordingly, hundreds of compounding pharmacists like Franck's—who had long been engaged in "traditional pharmacy ***1249** compounding" under the watchful eyes of state boards of pharmacy—invested in and grew their practices based on their expectations that compounding practices consistent with state law were authorized under federal law. (*See* Franck Dec. ¶ 65.) [88] But although the FDA generally deferred to the states with regard to "traditional compounding," and brought no enforcement actions against the numerous pharmacies nationwide engaged in bulk compounding for non food-producing animals, the agency has, since *9/1 Kg. Containers,* asserted that it possessed the statutory authority to regulate the practice. As a result, state-licensed veterinarians and pharmacists have, with the FDA's blessing, been "living in sin" (according to the FDA) for over twenty years. *Med. Ctr.,* 536 F.3d at 400. [89]

The FDA says that it does adequately account for the continued practice of traditional pharmacy compounding through the judicious exercise of its enforcement discretion. [90] The FDA does not dispute that the practice of pharmacy compounding, including compounding of animal drugs from bulk, was widespread at the time FDCA was enacted (or even that it remains so today). However, it dismisses the notion that this long-standing practice (and the agency's long-standing failure to enforce against it) somehow undermines its current enforcement

authority. It notes that the Fifth Circuit rejected the same argument on the basis of FDA's enforcement discretion, which prevented the *reductio ad absurdum* of eradicating the widespread and accepted process of compounding. Thus, the FDA says, "the specter that [D]efendants present of the whole [pharmacy] industry behind bars is farfetched hyperbole. FDA has consistently exercised its enforcement discretion against compounding pharmacies in a manner that clearly demonstrates that it has no intention of shuttering the entire industry." (Doc. 54 at 17.)

Although that argument was appropriately accepted by the Fifth Circuit under the procedural posture of that case, it cannot prevail here. Had the Fifth Circuit upheld the district court's implied exemption of all pharmacists from the FDCA's new drug approval process, it would have handcuffed the FDA's ability to police the line between traditional compounding and manufacturing because *all* compounded drugs, even those prepared by pharmacists manufacturing in the guise of compounding, would have been exempt from FDA enforcement. Thus, because the Fifth Circuit ***1250** recognized that the FDA could properly draw a line between compounding and manufacturing, the court relied upon the FDA's enforcement discretion as a counterpoint to the agency's otherwise unfettered authority. *Med. Ctr.,* 536 F.3d at 399 ("Construing the FDCA to give the FDA authority *over compounding* would thus not necessarily 'lead to a result so bizarre that Congress could not have intended it.' ") (emphasis added and citation omitted). [91]

Here, the FDA's authority to regulate pharmacy compounding as a disguise for manufacturing is not at issue. Rather, utilizing this first-of-its-kind enforcement action, the FDA seeks to expand its statutory authority by enjoining an individual pharmacy which is engaged in traditional pharmacy compounding of animal drugs in compliance with state law. In so doing, the FDA overreaches. *See W. States,* 535 U.S. at 369–70, 122 S.Ct. 1497 ("[I]t *would not make sense* to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process [because] requiring such testing *would force pharmacists to stop providing compounded drugs* ") (emphasis added).

Another potential anomaly (not presented to the Fifth Circuit) is in sharp relief here. If the FDA's position is correct, Congress intended to give the agency the authority to require traditionally compounded medications for non food-producing animals to go through the FDA's lengthy and involved new drug approval process but declined to require it for compounded medications prescribed for human beings. This is simply too much for a public health statute like the FDCA to bear.

As a result, though § 321(v)'s "new animal drug" definition affords the FDA license to enforce against pharmacists who manufacture in the guise of compounding, Congress did not, by any remaining contextual ambiguity, give the FDA the authority to enjoin traditional pharmacy compounding of animal drugs, a practice never before regulated by a federal agency and never mentioned in the FDCA. *See ABA I,* 430 F.3d at 469. The FDA is certainly statutorily authorized to draw clear distinctions between manufacturing and compounding generally. *See W. States,* 535 U.S. at 372–73, 122 S.Ct. 1497. However, what the FDA seeks to do here is reinterpret the FDCA to allow it to *eradicate* the line between manufacturing and traditional compounding of animal medications. Its wholesale assertion of authority over traditional pharmacy compounding in the context of a pharmacist-veterinarian-patient relationship is contrary to congressional intent. *See Gonzales,* 546 U.S. at 267, 126 S.Ct. 904; *Brown & Williamson,* 529 U.S. at 160, 120 S.Ct. 1291. Thus, the Court concludes that the FDA lacks the statutory authority it seeks to exercise here.

4. Chevron Step Two

However, to the extent that the FDCA could be interpreted as being ambiguous in such a way as to allow deference to the FDA's statutory construction, the agency's interpretation would fail, for many of the same reasons, at *Chevron* Step Two. That is, even if FDA's attempt to regulate traditional pharmacy compounding fills a gap in ***1251** the FDCA, the agency's expansive view of its statutory authority is not sufficiently reasonable to survive *Chevron* Step Two given the requisite level of deference. *See ABA I,* 430 F.3d at 471–72.

The FDA asserts that the Court should, in accordance with *Chevron,* "defer to the agency's interpretation of any ambiguity in its governing statute." (Doc. 60 at 9.) "*Chevron* deference, however, does not necessarily apply to every interpretation offered by an agency." *Sierra Club,*

541 F.3d at 1265 n. 3; *see also United States v. Mead Corp.,* 533 U.S. 218, 228, 121 S.Ct. 2164, 150 L.Ed.2d 292 (2001) ("The fair measure of deference to an agency administering its own statute has been understood to vary with the circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position") (citations and footnotes omitted); *Gonzales,* 546 U.S. at 258, 126 S.Ct. 904 ("*Chevron* deference ... is not accorded merely because the statute is ambiguous and an administrative official is involved"). As a result, "[d]eference in accordance with *Chevron* ... is warranted only 'when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was *promulgated* in the exercise of that authority.' " *Gonzales,* 546 U.S. at 255–56, 126 S.Ct. 904 (quoting *Mead,* 533 U.S. at 226–27, 121 S.Ct. 2164) (emphasis added). "Otherwise, the interpretation is 'entitled to respect' only to the extent it has the 'power to persuade.' " *Id.* at 256, 126 S.Ct. 904 (quoting *Skidmore v. Swift & Co.,* 323 U.S. 134, 140, 65 S.Ct. 161, 89 L.Ed. 124 (1944)).

[12] When Congress has generally conferred authority on an agency, Congress expects the agency to speak with the binding authority of law "when it addresses ambiguity in the statute or fills a space in the enacted law," even if there was no congressional intent for a particular result. *Mead,* 533 U.S. at 229, 121 S.Ct. 2164. In this regard, "[i]t is fair to assume generally that Congress contemplates administrative action with the effect of law when it provides for a relatively formal administrative procedure *tending to foster the fairness and deliberation that should underlie a pronouncement of such force.*" *Id.* at 230, 121 S.Ct. 2164 (emphasis added); *see also Christensen v. Harris County,* 529 U.S. 576, 587, 120 S.Ct. 1655, 146 L.Ed.2d 621 (2000) (suggesting that the "rigors of the Administrative Procedure Act, including public notice and comment" warrant greater deference). Accordingly, most courts have afforded the high level of *Chevron* deference to agency interpretations which result from notice-and-comment rule-making—namely regulations—or formal adjudications. *Mead,* 533 U.S. at 229–30, 121 S.Ct. 2164; *see also Miccosukee Tribe of Indians of Fla. v. United States,* 566 F.3d 1257, 1272–73 (11th Cir.2009) ("Notice-and-comment rulemaking is [ ] 'significant ... in pointing to *Chevron* authority' ") (citing *Mead*).

Even if Congress had implicitly delegated authority to the FDA to regulate traditional pharmacy compounding of animal medications, the FDA has never promulgated regulations to this effect through notice-and-comment rule-making. Rather, as discussed *supra,* the agency has instead utilized non-binding Compliance Policy Guides, such as the 1996 and 2003 Guides, to assert its authority. The Supreme Court in *Christensen* stated that "policy statements, agency manuals, and enforcement guidelines, all of which lack the force of law [ ] do not warrant *Chevron*-style deference." 529 U.S. at 587, 120 S.Ct. 1655. Accordingly, the Eleventh Circuit has held that "[i]nterpretations not the product of 'a formal adjudication or notice-and-comment rulemaking ... which lack ***1252** the force of law' do not warrant *Chevron*-style deference, but are still 'entitled to respect ... to the extent that those interpretations have the power to persuade.' " *Sierra Club,* 541 F.3d at 1265 n. 3 (quoting *Christensen,* 529 U.S. at 587, 120 S.Ct. 1655); *see also Wilderness Watch v. Mainella,* 375 F.3d 1085, 1091 n. 7 (11th Cir.2004) ("[W]hen ... the agency interpretation does not constitute the exercise of its formal rule-making authority, we accord the agency consideration based upon the factors cited in *Skidmore* [ ]: 'the *thoroughness evident in [the agency's] consideration, the validity of its reasoning, its consistency with earlier and later pronouncements,* and all those factors which give it power to persuade, if lacking power to control' ") (emphasis added and other citations omitted). Because the FDA seeks to enforce a prohibition that it has not delineated through notice-and-comment rule-making, *Skidmore* deference is appropriate here. For the reasons set forth *supra,* Sec. IV(B)(4), and for the additional reasons below, FDA's statutory interpretation lacks the "power to persuade." *Skidmore,* 323 U.S. at 140, 65 S.Ct. 161.

The FDA seeks to prohibit Franck's traditional bulk compounding of animal drugs for non food-producing animals because the practice "undercut[s] approved drugs by manufacturing unapproved, compounded bulk drugs that are less expensive alternatives with the same intended use." (Doc. 54 at 5.) However, this unsupported assertion is directly contradicted by the record evidence in this case.[92] Indeed, this only serves to illustrate a significant problem with the FDA's position: the agency has never attempted to test its views concerning bulk compounding for non food-producing animals by notice and comment review. The agency's failure to allow for public comment on the issue caused consternation to the numerous

Congressmen and Senators who protested the agency's issuance of the 2003 Guide. The FDA promised that it would publish new guidance, then didn't. The FDA's behavior on this issue is thus reminiscent of the FTC's recent attempt to regulate identity theft in the attorney-client context:

> The Commission's interpretation is also not dispositive of the issue because it represents an interpretation that evolved after the period for notice and comment closed, and without any fact-finding justification for the decision. To be clear, the Court is not saying that an agency with congressional authority cannot develop, apply, or adapt any reasonable interpretation it deems appropriate. *See Rust v. Sullivan,* 500 U.S. 173, 186, 111 S.Ct. 1759, 114 L.Ed.2d 233 (1991) (finding that an agency's revised interpretation may still receive deference because "[a]n agency is not required to establish rules of conduct [that once established must] last forever" (citations and internal quotations omitted)); *see also Skidmore,* 323 U.S. at 140, 65 S.Ct. 161 (indicating that whether an agency's interpretation of a regulation is "consisten[t] with earlier and later pronouncements" may factor into whether an ***1253** agency's interpretation has the "power to persuade"). Rather, it is the Court's conclusion that the Commission's interpretation is not persuasive *because it does not correspond with any agency factual findings supporting the need to redress identity theft associated with the legal profession and why existing regulations of the profession are inadequate, assuming a problem even exists.* From the record before the Court (or more accurately the lack of a record), *the best that can be gleaned is that identity theft in the attorney-client context is only a theoretical problem, especially given the role of state professional codes of conduct and other ethical codes to which attorneys must abide, and the Court cannot conclude that it is an actual problem given the absolute lack of any legislative, regulatory or other evidentiary findings that have been brought to the Court's attention.*
>
> *ABA II,* 671 F.Supp.2d at 85–86 (emphasis added, certain citations and footnote omitted).

Similarly, traditional bulk compounding of animal drugs only "theoretically" threatens the FDCA's new drug approval process, because the FDA has not undertaken the necessary steps to find the facts, explain its rationale and allow for public discourse on the issue. "[W]here an agency has articulated no reasoned basis for its decision—where its action is founded on unsupported assertions or unstated inferences—we will not abdicate the judicial duty carefully to review the record to ascertain that the agency has made a reasoned decision based on reasonable extrapolations from some reliable evidence." *Tripoli Rocketry Ass'n v. Bureau of Alcohol, Tobacco, Firearms & Explosives,* 437 F.3d 75, 81, 83 (D.C.Cir.2006) ("The fatal shortcoming of [the agency's] position is that it never reveals how it determines that [the standard it employed] ... reflects reasoned decision making"). "[W]e cannot, under the guise of deference, sanction an agency's use of a standard that the agency has not adequately explained." *Federal Exp. Corp. v. Holowecki,* 552 U.S. 389, 416, 128 S.Ct. 1147, 170 L.Ed.2d 10 (2008) (Thomas, J., concurring).

Just as it has failed to explain its prohibition of bulk compounding of animal drugs via a "relatively formal administrative procedure," *Mead,* 533 U.S. at 230, 121 S.Ct. 2164, the FDA has chosen not to dispute Franck's showing in this case that the practice is an essential component of veterinary medicine. It is thus undisputed that hundreds of pharmacies currently compound animal medications from bulk under the imprimatur and regulation of state law, and have done so without interference by the FDA for many years. The undisputed evidence in this record also shows that allowing the FDA to enjoin a pharmacist's traditional, state-authorized practice of bulk compounding of animal drugs could destabilize the pharmacy profession and leave many animal patients without necessary medication. *See supra* at 1216–19. Such a result would be especially troublesome because the FDA's longstanding policy has been to permit, and even promote, pharmacists' compounding from bulk ingredients. The FDA cannot simply upset the expectations it helped to create through decades of inaction without explanation,[93] especially where its asserted ***1254** expansion of authority impacts the federal-state balance and potentially subjects many individuals and companies to criminal liability. This conclusion is supported by the both the plain statement rule and the rule of lenity.

The essence of the plain statement rule is captured by the D.C. Circuit in *ABA I.* In rejecting the FTC's assertion of authority to regulate attorneys, the Court stated:

> It is undisputed that the regulation of the practice of law is traditionally the province of the states. Federal

law "may not be interpreted to reach into areas of State sovereignty unless the language of the federal law compels the intrusion." *City of Abilene v. FCC,* 164 F.3d 49, 52 (D.C.Cir.1999). Otherwise put, "if Congress intends to alter the 'usual constitutional balance between the States and the Federal Government,' it must make its intention to do so 'unmistakably clear in the language of the statute.' " *Will v. Michigan Dep't of State Police,* 491 U.S. 58, 65, 109 S.Ct. 2304, 105 L.Ed.2d 45 (1989) (quoting *Atascadero State Hospital v. Scanlon,* 473 U.S. 234, 242, 105 S.Ct. 3142, 87 L.Ed.2d 171 (1985)).

ABA I, 430 F.3d at 471–72.

In *Gregory v. Ashcroft,* 501 U.S. at 461, 111 S.Ct. 2395, the Supreme Court held that "[t]his plain statement rule is nothing more than an acknowledgment that the States retain substantial sovereign powers under our constitutional scheme, powers with which Congress does not readily interfere." The same principles are applicable here. The FDA has pointed to no "unmistakably clear" statement that Congress intended the FDA's authority to extend beyond the manufacturer-compounder line identified by the Supreme Court in *Western States* and into the realm of traditional pharmacy compounding. The FDA is correct in noting that Congress may directly regulate some matters already subject to state regulation, "but it is also true that Congress does not tend to interject itself into an arena where it hasn't generally ventured without explicit explanation hoping that the states will not notice the usurpation of their authority." *ABA II,* 671 F.Supp.2d at 87 (citing *ABA I,* 430 F.3d at 472).[94] To paraphrase the D.C. Circuit as applied to this case: The states have regulated the traditional practice of pharmacy compounding, which includes compounding of animal drugs from bulk ingredients, throughout the history of the country; the federal government has not. This is not to conclude that the federal government could not do so. The Court simply concludes that it is not reasonable for an agency to decide that Congress has chosen such a course of action in language that is, even charitably viewed, at most ambiguous. *See ABA I,* 430 F.3d at 472.

[13] There is yet another troubling ramification of FDA's position in this case: because the FDCA provides for both criminal and civil penalties for any act prohibited by 21 U.S.C. § 331, *see id.* § 333(a), the compounding of *one* non food-producing ***1255** animal medication from bulk ingredients subjects a state-licensed pharmacist—whether the pharmacist's practice consists of a "large, interstate operation" or a "Mom–and–Pop" shop—to the criminal penalties of the FDCA. Simply relying on the good graces of the FDA's "enforcement discretion" will not suffice. Such a "standard" openly invites arbitrary enforcement, which is antithetical to our system of criminal justice. It is to protect against such arbitrary enforcement that the rule of lenity requires that when a statute carries criminal penalties, any ambiguities must be interpreted in the defendant's favor to avoid "prohibit[ing] more conduct or punish[ing] more severely than Congress intended." *Wright,* 607 F.3d at 717 (citing cases).[95] The rule applies in this case because although FDA did not bring this enforcement action under the FDCA's criminal provisions, it could have; the statute must be interpreted consistently in both the criminal and civil contexts. *See Leocal v. Ashcroft,* 543 U.S. 1, 11–12 n. 8, 125 S.Ct. 377, 160 L.Ed.2d 271 (2004) (explaining that "the rule of lenity applies" to the Court's interpretation of a statute even in noncriminal cases "[b]ecause we must interpret the statute consistently, whether we encounter its application in a criminal or noncriminal context").

V. Conclusion

The Court appreciates the FDA's difficult task in protecting the health of both humans and animals. The Court further understands that the FDCA has given the FDA broad regulatory and enforcement powers to implement this mandate and that the courts must afford due deference to the FDA's interpretation and implementation of the FDCA. Nevertheless, the FDA's authority is not unlimited and courts have a role to play in determining whether the agency's actions exceed the statutory powers given to it by Congress.

The FDA has long been on notice that its statutory authority to regulate traditional, state-licensed veterinary pharmacy compounding was questionable. Indeed, in 2004, the FDA acknowledged the concern:

> FDA has received numerous letters from veterinarians, pet owners, compounding pharmacists, and associations expressing concern that the [2003 Guide] lacks sufficient clarity on the circumstances in which veterinary compounding, particularly from bulk drugs, would

> be permitted. Many of the letters also disagreed with the current policy, stating that it was not within FDA's legal authority, and complained about the lack of prior public comment. After meeting with several groups and considering the comments in the letters it has received FDA concluded that issuing a revised CPG is appropriate.

FDA to Revise Its Compliance Policy Guide on Veterinary Compounding, supra p. 1229. Rather than follow through with this sensible approach, the FDA apparently abandoned it. [96] Instead, it has decided ***1256** to proceed with this enforcement action, asserting a "maximalist" interpretation of its authority. However, the FDCA does not support the FDA's action. The Court holds that, in enacting the FDCA in 1938, Congress did not intend to give the FDA *per se* authority to enjoin the long-standing, widespread, state-regulated practice of pharmacists filling a veterinarian's prescription for a non food-producing animal by compounding from bulk substances. [97]

Accordingly, it is hereby

ORDERED:

1. The United States' Motion for Summary Judgment (Doc. 54) is **DENIED.**

2. Defendants' Motion for Summary Judgment (Doc. 56) is **GRANTED** to extent described in this Order.

3. The United States is not entitled to the injunction it seeks.

4. Judgment for Franck's and against the United States shall be entered.

5. The Clerk should close the file.

All Citations

816 F.Supp.2d 1209

Footnotes

1 As will be discussed in greater detail *infra,* the FDA is not challenging Franck's practice of human drug compounding.

2 The term "bulk," used in this context, does not refer to size, volume, or quantity; rather, it refers to the raw chemical materials used in the compounding process. *See, e.g.,* 21 C.F.R. § 207.3(a)(4) (defining "bulk drug substance" as "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug ...."). Compounding from bulk ingredients is sometimes referred to as "bulk compounding."

3 Director of the Florida District Office, United States Food and Drug Administration.

4 On this third point, Franck's noted that it would provide such labeling even though it "does not compound for any food-producing animals." *Id.* at 2.

5 James Powers, a member of the Florida Board of Pharmacy's two-person probable cause panel that preliminarily reviewed the polo pony incident, declared that: "After a thorough and careful review of all the facts, the Florida Board deemed the incident a misfill, a mathematical error in converting an ingredient. Nothing in our extensive investigation uncovered any information suggesting that the polo horse incident resulted merely because Franck's compounded the medication using bulk chemical ingredients." Doc. 31, Declaration of James B. Powers ("Powers Dec.") at ¶ 43.

6 Rather, the FDA's concerns primarily involved perceived quality assurance and training issues. *Id.*

7 More specifically, the FDA's complaint prays that this Court: "Permanently and perpetually restrain and enjoin, under 21 U.S.C. § 332(a), Defendants ... from compounding, manufacturing, processing, packing, labeling, holding, or distributing articles of drug for use in animals, unless and until Defendants obtain appropriate FDA approvals for their drugs, or meet an appropriate exemption to the approval requirements ...." Doc. 1 at 11.

8 The parties initially filed a number of declarations in connection with the FDA's motion for preliminary injunction. At the parties' request, all such earlier-filed record materials were deemed part of the summary judgment record. Doc. 49 ¶ 7; Doc. 53 ¶ 3.

9 Shortly before the August 18, 2010 preliminary injunction hearing, the FDA submitted two three-page affidavits purporting to show that Franck's had engaged in additional violative conduct. The first contains allegations that a Franck's pharmacist

compounded a medication (Acetyl–D) for a veterinarian after Franck's had voluntarily suspended compounding pending the outcome of this case. *See* Doc. 24, Declaration of Dr. Robert C. Saunders. The second asserts that the Acetyl–D compound was an unapproved generic formulation of the commercially available drug product Adequan. *See* Doc. 23, Declaration of Dr. William T. Flynn. The ink was barely dry on Dr. Saunders' declaration when he filed a corrected declaration on behalf of Franck's, providing additional facts which demonstrated that *Franck's had not been the pharmacy that filled the prescription in question* and that the FDA had either (at best) misconstrued or (at worst) mischaracterized his statements. *See* Doc. 41, Supplemental Declaration of Dr. Robert B. Saunders; *see also* Doc. 39, Declaration of Kenneth Pettengill (the pharmacist who filled the prescription); Doc. 40, Declaration of Alexis Ells (the client for whom it was filled).

10 Senior Advisor for Science Policy for FDA's Center for Veterinary Medicine ("CVM").

11 Director of Clinical Pharmacy Services at North Carolina State University College of Veterinary Medicine; Society of Veterinary Hospital Pharmacists' 2003 representative on FDA Ad Hoc Committee on Veterinary Compounding.

12 Licensed pharmacist; Editor–in–Chief of International Journal of Pharmaceutical Compounding ("IJPC"); former member of FDA's Pharmacy Compounding Advisory Committee.

13 President, Marion County (Florida) Veterinary Medical Association.

14 Equine veterinarian and owner of Harthill Company, a veterinary medicine practice located at Gate 5 of Churchill Downs.

15 Co–Chair, Hunton & Williams LLP Food and Drug Practice Group; former Chief Counsel of the FDA.

16 Thus, for example, despite the FDA's unsupported implications to the contrary, the record evidence shows that Franck's has a reputation for *refusing* to compound drugs that are commercially available, *see* Pelphrey Doc. ¶ 21, and has adequate safeguards against such an occurrence, *see* Davidson Dec. ¶ 85; Franck Dec. ¶¶ 32–34. The record is also undisputed that Franck's only compounds within the context of a valid pharmacist-prescriber-patient relationship, Franck Dec. ¶¶ 30, 44, 86, and in so doing provides an essential service that is part of the practice of veterinary medicine, Davidson Dec. ¶ 35; Allen Dec. ¶ 18.

17 Though this definition, taken from the Supreme Court's opinion in *Western States,* captures the overarching principles of compounding, there is no standard definition of the practice. *See, e.g.,* Fla. Admin. Code Ann. 64B16–27.700 (" 'Compounding' is the professional act by a pharmacist ... employing the science or art of any branch of the profession of pharmacy, incorporating ingredients to create a finished product for dispensing to a patient ....; and shall specifically include the professional act of preparing a unique finished product containing any ingredient or device"); Allen Dec. ¶ 13 ("Pharmacy compounding is the preparation of a customized medicine that has been prescribed by a doctor in the course of the professional practice of medicine, and which is prepared by a state-licensed pharmacist"); Davidson Dec. ¶ 33 ("Compounding is the preparation of components into a medication either pursuant to a valid prescription based on a valid [practitioner]-client-patient-relationship or for the purpose of dispensing to licensed physicians and veterinarians for office use, where state law permits such use"); Flynn Dec. ¶ 15 ("Drug compounding is a practice in which a pharmacist prepares medications that are not commercially available, for the unique needs of an individual patient").

18 See Florida Pharmacy Act, Fla. Stat. §§ 465.001 *et seq.* (creating the Florida Board of Pharmacy and conferring upon the Board the duty to regulate the practice of pharmacy within the state); *id.* § 465.003(13) (" 'Practice of the profession of pharmacy' *includes compounding,* dispensing, and consulting concerning contents, therapeutic values, and uses of any medicinal drug ....") (emphasis added).

19 *See* Fla. Admin. Code Ann. 64B16–27.700(1) ("Compounding includes: (a) The preparation of drugs or devices in anticipation of prescriptions based on routine, regularly observed prescribing patterns [;] (b) The preparation pursuant to a prescription of drugs or devices which are not commercially available ....")

20 *See, e.g., Prof'ls and Patients for Customized Care v. Shalala,* 56 F.3d 592, 593 (5th Cir.1995) ("Pharmacies have long engaged in the practice of traditional compounding, the process whereby a pharmacist combines ingredients pursuant to a physician's prescription to create a medication for an individual patient...."); Bradshaw Dec. ¶ 45 ("Traditional pharmacy compounding ... is generally understood to mean 'the preparation of Components into a Drug product (1) as the result of a Practitioner's Prescription Drug Order based on the Practitioner/patient/Pharmacist relationship in the course of professional practice ....' ") (quoting National Association of Boards of Pharmacy, *Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy,* Appx. B, subpt. A(a) at 207 (Aug. 2011), *available at* http://www.nabp.net/publications/model-act/ (last visited September 12, 2011); Doc. 54 (FDA's Motion for Summary Judgment) at 4 ("Traditionally, pharmacists have extemporaneously compounded necessary quantities of drugs upon receipt of a valid prescription in response to an individual patient's medical need, or in very limited quantities based on documented records of valid prescriptions generated in an established physician-patient-pharmacy relationship for human drugs and a veterinarian-client-patient-pharmacy relationship for animal drugs").

21 *See also* Allen Dec. ¶ 18 ("Because each animal patient is different, it has unique and specific needs that make compounded medications a vital part of quality veterinary medicine. In fact, for many animal patients, a customized, compounded medication prescribed by licensed veterinarians and prepared by a trained, licensed compounding pharmacist is the best practice for treating the animal patient. *If compounded medications are not available, there are a large number of animal patients that would not have access to life-saving drugs* ") (emphasis added); Pelphrey Dec. ¶¶ 8, 10 ("Compounding is an essential part of my veterinary medicine practice. Without compounding, many of my [equine] patients would not receive the medication that is needed to appropriately treat their unique needs because *many of my patients cannot be treated with commercially available drug products* ") (emphasis added); *but see* Flynn Dec. ¶¶ 5, 26 (asserting that while there is an "*insufficient variety of approved medications*", "the unchecked proliferation" of compounding practices such as Franck's "*may* create disincentives for drug sponsors to develop necessary and useful animal drugs ....") (emphasis added).

22 Bulk ingredients require a certificate of analysis that includes detailed information not available for finished drug products, including the concentration and specification of all ingredients, expiration date, manufacture date, method of analysis, analysis results, and storage conditions. Allen Dec. ¶ 26.

23 *See id.* ¶ 21 ("The FDA-approved, commercially available drug products are available only in limited strengths ... [I]t is unlikely, for instance, that a 5,000 pound elephant can be properly treated with the same strength medication as a 10–pound feline").

24 Compounding from finished drug products is inefficient because it requires a pharmacist to, in essence, "reverse engineer" the finished product into its unfinished form so as "to identify the finished product's formulation parameters, to distinguish and quantify the ingredients of the finished product (i.e., the active pharmaceutical ingredients, excipients, etc.) and to separate out the distinct ingredients of the finished product. The compounding pharmacist then uses (or removes) the 'separated' ingredients to compound the preparation in the prescribed dosage, formulation, and strength." Franck Dec. ¶ 45.

25 For example, FDA-approved human drugs are sometimes removed from the market because of safety reasons not associated with the use of the drug in animals. *See* Davidson Dec. ¶¶ 56–61 (citing Pergolide (used off-label to treat Cushing's syndrome in horses) and Cisapride (used off-label to treat feline megacolon) as examples of discontinued drugs with no current substitutes, and noting that "[i]f compounding pharmacists [we]re not able to compound these medically useful and/or necessary medications from bulk ingredients, animals would needlessly suffer from chronic or catastrophic illnesses").

26 At the time the FDCA was enacted, the USP contained monographs with instructions on how to compound medications from bulk ingredients; the USP continues to authorize compounding when the monographs are followed. Allen Dec.¶¶ 33–48; *see also* Bradshaw Dec.¶ 17. The standards of the USP, which the 1938 FDCA recognized as a baseline for the strength, quality, purity, and packaging of pharmaceutical ingredients for compounded drugs, are legally enforceable by the FDA and state boards of pharmacy. Allen Dec. ¶¶ 33–35. Bulk ingredients for a which a monograph is provided in the USP are required to conform to that monograph. *Id.* ¶ 27. Many FDA-approved finished drugs, on the other hand, do not have USP monographs, making it "difficult for pharmacists to determine whether a compounded preparation from finished drug products falls within the desired range of USP purity, potency, and quality compounding standards." *Id.* ¶ 32.

27 *See* Fla. Admin. Code Ann. 64B16–27.700(1) ("Compounding includes ... (c) The preparation of commercially available products from bulk when the prescribing practitioner has prescribed the compounded product on a per prescription basis and the patient has been made aware that the compounded product will be prepared by the pharmacist...."). Florida regulations also provide standards of practice for compounding from bulk ingredients. *See* Fla. Admin. Code Ann. 64B16–27.1001(2) (stating that a pharmacist must personally interpret incoming orders for bulk solutions; compound or be physically present for the compounding of bulk solutions; "[p]hysically examine, certify to the accuracy of the final preparation, thereby assuming responsibility for the final preparation"; and "[s]ystemize all records and documentation of processing in such a manner that professional responsibility can easily be traced to a pharmacist").

28 "Because Florida law explicitly permits bulk compounding, I can say from my experience as a member of the Florida Board [of Pharmacy] that many, if not all, compounding pharmacies in Florida compound drug products from bulk ingredients, and are permitted to do so under Florida law." Powers Dec. ¶ 24; *see also* Stoothoff Dec. ¶ 14 ("[N]umerous pharmacies in Florida compound medications for veterinary use from bulk ingredients. In fact, there are at least four other local pharmacies in Marion County aside from Franck's that routinely compound medications for use in animals from bulk ingredients").

29 *See also* Davidson Dec. ¶¶ 41, 54 (noting that "a large segment of the compounding industry has been built around the practice of compounding animal medications from bulk ingredients"); Pelphrey Dec. ¶¶ 15, 18 ("To my knowledge,

compounding medication for use in non-food producing animals from bulk ingredients is an everyday practice for compounding pharmacies. In fact, all the compounding pharmacies I work with regularly compound medications from bulk ingredients.... In my opinion, the equine medicine community has a compelling interest in ensuring that compounding pharmacies continue the long-standing practice of compounding medically necessary medications from bulk ingredients when appropriate in response to a prescription made by a licensed veterinarian").

30 Likewise, and more pertinent to this case, the FDCA defines "new animal drug" as "any drug intended for use for animals other than man ... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(v)(1).

31 As is the case with a "new drug," the FDCA empowers the FDA to require approval of any "new animal drug." If it has not been approved by the FDA, a "new animal drug" is "unsafe" under 21 U.S.C. § 360b(a)(1) and thus "adulterated" under 21 U.S.C. § 351(a)(5). An unapproved "new animal drug" lacking "adequate directions for use" is "misbranded" under 21 U.S.C. § 352(f) and FDA regulations. *See* 21 C.F.R. 201.122. Hence, the FDA asserts that to avoid being deemed "adulterated," "unsafe," or "misbranded," a compounded drug product must either go through the new animal drug approval process or fall outside the definition of "new animal drug."

32 In reality, FDA had begun to address this concern—in a slightly different but related context—through enforcement actions prior to its issuance of the 1992 Guide. Specifically, the FDA asserted that bulk drugs held by a middleman for compounding by veterinarians were unlawfully misbranded under the FDCA, a position ultimately upheld by the Seventh Circuit in *9/1 Kg. Containers,* 854 F.2d at 179. A year later, the Third Circuit upheld the FDA's regulatory authority to limit the sale of new bulk drugs exclusively to holders of "new animal drug applications," a definition that excluded veterinarians. *United States v. Algon Chemical, Inc.,* 879 F.2d 1154, 1155 (3d Cir.1989).

33 The 1992 Guide explained that "[t]he [FDA] has initiated enforcement action when pharmacy practice extends beyond the reasonable and traditional practice of a retail pharmacy," and that "[t]he courts have upheld FDA's interpretation in those cases." *Id.* at 3 (citing *United States v. Sene X Eleemosynary Corp.,* 479 F.Supp. 970 (S.D.Fla.1979); *Cedars N. Towers Pharm., Inc. v. United States,* [1978–79 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) para. 38,200 at 38,826 (S.D.Fla. Aug. 28, 1978)). The Guide also cited *Algon,* 879 F.2d 1154; *9/1 Kg. Containers,* 854 F.2d 173; and *United States v. Rutherford,* 442 U.S. 544, 99 S.Ct. 2470, 61 L.Ed.2d 68 (1979) for their analysis "*regarding limitations on sale of unapproved and otherwise unlawful products to licensed practitioners.*" *Id.* (emphasis added).

34 The "Background" section of the 1992 Guide, in discussing FDA's concern about manufacturing in the guise of compounding, highlighted "establishments with retail pharmacy licenses" which, among other things, "receive and use in large quantity bulk drug substances to manufacture unapproved drug products and to manufacture drug products in large quantity, in advance of receiving a valid prescription for the products." 1992 Guide at 2. Later, the FDA recounted an inspection of a company "operating with a pharmacy license" which "revealed that the firm had hundreds of bulk ingredients on hand to manufacture about 165 different products," a majority of which had been compounded in advance of a valid prescription. *Id.* at 3.

35 Prior to AMDUCA, section 360b provided that a "new animal drug" was "unsafe" unless it was subject to an approved application and the drug, its labeling, *and its use* conformed to the application. *See* Bradshaw Dec. ¶ 37. As a result, the use of a "new animal drug" in a manner different from that set forth in the drug's approved application (i.e., for an off-label or extra-label use) resulted in the drug being classified as "unsafe" and "adulterated" under the FDCA. *Id.*

36 AMDUCA's implementing regulations also reflect a clear policy distinction between extralabel uses in so-called "food-producing animals" (e.g., cows) and "non food-producing animals" (e.g., horses). *Compare* 21 C.F.R. § 530.21(a) ("FDA may prohibit the extralabel use of an approved new animal or human drug or class of drugs in food-producing animals if FDA determines that: (1) [a]n acceptable analytical method needs to be established and such method has not been established or cannot be established; or (2) [t]he extralabel use of the drug or class of drugs presents a risk to the public health") *with* 21 C.F.R. § 530.30(a) ("Because extralabel use of animal and human drugs in non food-producing animals *does not ordinarily pose a threat to the public health,* extralabel use of animal and human drugs is permitted in non food-producing animal practice except when the public health is threatened") (emphasis added).

37 As support for this interpretation, the 1996 Guide asserted that "[t]wo Federal Appeals Court decisions, *Algon* and *9/1 Kg. Containers,* affirmed the FDA position that the FDCA does not permit veterinarians to compound unapproved finished drug products from bulk drugs, unless the finished drug is not a new animal drug. The principle established by the court applies equally to compounding by pharmacists." *Id.* Notably, the FDA similarly asserted that compounding a new animal drug from "an approved ... human or animal drug" would result in a violation of the FDCA, but acknowledged that this would no longer be the case when AMDUCA became effective. *Id.*

38 In turn, a "legitimate practice" was defined as follows:

> (a) *Pharmacist: A person licensed and operating in conformity with state law, and dispensing in response to a valid prescription.*
>
> (b) Veterinarian: A person licensed and operating in conformity with state law, and prescribing or dispensing in response to a valid Veterinarian–Client–Patient Relationship (VCPR).

Id. (emphasis added); *cf. supra* n. 20, 27.

39 Thus, much like the FDA's regulations implementing AMDUCA, *supra* n. 36, the 1996 Guide draws both a policy and enforcement line between compounding for food and non food-producing animals. *See* 1996 Guide at 31,851 ("In general, the agency will place its highest regulatory priority on compounding products for use in food animals"). As discussed *infra,* the FDA later eliminated the food/non-food animal distinction from its guidance without explanation.

40 The Guide noted that bulk drug substances used to compound medication for nonfood animals "would ordinarily be expected to be in small packages that meet or exceed USP standards," and that compounding of any such substance "should be performed in accordance with current standards of pharmaceutical practice (including referral to compendial monographs or established pharmacy textbooks)." *Id.*

41 *Cf. W. States,* 535 U.S. at 364, 122 S.Ct. 1497 ("Congress *turned portions of [the 1992 Guide] into law* when it enacted the FDAMA in 1997. The FDAMA, which amends the FDCA, exempts compounded drugs from the FDCA's 'new drug' requirements and other requirements provided the drugs satisfy a number of restrictions") (emphasis added).

42 In enacting FDAMA, Congress also recognized that regulation of compounding was historically the province of the States: "States currently have the authority to license pharmacists and regulate pharmacies, including the scope of pharmacy practice. All states include compounding as a core component of the profession of pharmacy." Food and Drug Modernization and Accountability Act of 1997, S.Rep. No. 105–43 at 67 (1997).

43 Section 353a(b)(1)(A) authorizes pharmacists to compound drug products "using bulk drug substances" as defined in 21 C.F.R. § 207.3 (*see supra* n. 2) so long as the bulk drugs comply with the applicable USP monograph or, if no monograph exists, the bulk drugs are components of drugs approved by the FDA. 21 U.S.C. § 353a(b)(1)(A).

44 Although the Ninth Circuit deemed FDAMA non-severable, and therefore invalidated the amendment in its entirety, *see W. States Med. Ctr. v. Shalala,* 238 F.3d 1090, 1096–98 (9th Cir.2001), the Supreme Court declined to address the validity of the remaining non-advertising portions of FDAMA because the parties had not appealed the severability issue. *W. States,* 535 U.S. at 366, 122 S.Ct. 1497.

45 "For example, [said the Supreme Court,] the Government could ban the use of 'commercial scale manufacturing or testing equipment for compounding drug products.' It could prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received. It could prohibit pharmacists from '[o]ffering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.' Alternately, it could limit the amount of compounded drugs, either by volume or by numbers of prescriptions, that a given pharmacist or pharmacy sells out of state. Another possibility not suggested by the Guide would be capping the amount of any particular compounded drug, either by drug volume, number of prescriptions, gross revenue, or profit that a pharmacist or pharmacy may make or sell in a given period of time." *Id.* (quoting the 1992 Guide) (internal citations omitted).

46 *See* FDA Compliance Policy Guide Sec. 460.200, Pharmacy Compounding (May 2002) ("2002 Guide") (human drugs); FDA Compliance Policy Guide Sec. 608.400, Compounding of Drugs for Use in Animals (July 2003) ("2003 Guide") (animal drugs).

47 The 2002 Guide makes no mention of any public health concerns associated with compounded drugs, nor does it make sweeping assertions of the FDA's authority to regulate the practice. Rather, its "Discussion" section begins with the statement that "FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance." 2002 Guide at 2. Appended to this statement is the following footnote: "With respect to such activities, 21 U.S.C. 360(g)(1) exempts retail pharmacies from the registration requirements of the [FDCA]. The exemption applies to 'Pharmacies' that operate in accordance with state law and dispense drugs 'upon prescriptions of practitioners licensed to administer such drugs to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail.' *See also* 21 U.S.C. §§ 374(a)(2) (exempting pharmacies that meet the foregoing criteria from certain inspection provisions) and 353(b)(2) (exempting drugs dispensed by filling a valid prescription from certain misbranding provisions)." *Id.* at 2 n. 2.

48 In his declaration, Dr. Flynn (*supra* n. 10) recognized that the 2003 Guide removed the 1996 Guide's exemption for compounding from bulk drugs for non food-producing animals. Flynn Dec. ¶ 28. Dr. Flynn's explanation for this change is that "[t]he 1996 [Guide] was issued before the promulgation of the AMDUCA implementing regulations, which make no distinction between food and nonfood animals. [Thus,] the [2003 Guide] includes no such distinction." *Id. But see supra* n. 36 (comparing 21 C.F.R. § 530.21(a) to 21 C.F.R. § 530.30(a)).

49 The term "legitimate practice," which was defined in the 1996 Guide, *supra* n. 38, is replaced in the 2003 Guide with the undefined term "traditional pharmacy practice." In addition, the 2003 Guide's list of factors which might prompt FDA to consider an enforcement action do not contain any of the 1996 Guide's language of scale, e.g., "[p]reparation for sale of *large* quantities of unapproved new animal drugs on an *ongoing* basis," 1996 Guide at 34,851 (emphasis in original). As a result, the 2003 Guide subjects small-scale practitioners to the same potential enforcement scrutiny as large-scale manufacturers. *See* 2003 Guide at 4–5.

50 The FDA's official policy statement on FDAMA, as announced in the 2002 Guide, is that the entire amendment is invalid, *see* 2002 Guide at 2, and the FDA has never changed this guidance. If FDAMA were invalid, there would be no statutory exemptions for human drug compounding. Under that scenario, the 2002 Guide would reflect *the FDA's* policy decision to endorse traditional bulk compounding of human drugs. The disparate treatment of human and animal compounding in the 2002 and 2003 Guides thus appears at odds with the 2003 Guide's stated goal of ensuring "consistency of [the FDA's] policies with regard to compounding of drugs intended for use in humans and in animals," 2003 Guide at 3. Adding to the confusion, the FDA in this case takes the position-contrary to the 2002 Guide-that FDAMA is in fact valid (perhaps based on the Fifth Circuit's decision in *Medical Center?*) and that "[t]here is no statutory basis for extending the human drug compounding exemptions of FDAMA to animal drugs because Congress enacted distinct exemption schemes for compounding human and animal drugs." Doc. 54 at 16. This is significant, as FDAMA is even more permissive of bulk compounding of human drugs than the 2002 Guide. *See* 21 U.S.C. § 353a(b)(1)(A); *supra* n. 43.

51 With regard to human compounding, the Congressmen noted that "the [1992 Guide's presumption that pharmacy compounding was illegal led to the passage of legislation in 1997 [i.e., FDAMA] that underscored the right of patients to have medications compounded to meet their individual needs, performed in the context of a pharmacist-physician-patient relationship." *Id.*

52 While finalizing this Order, the Court, on August 1, 2011, asked the parties to advise whether the FDA had issued any revised guidance regarding animal drug compounding. Doc. 65. The FDA replied that it "has not revised [the 2003 Guide] since oral argument in this case, or issued any other guidance regarding animal drug compounding." Doc. 66 at 1. Rather, "[t]he agency has continued to monitor compliance with the [FDCA] consistent with the positions outlined in [the 2003 Guide]." *Id.* However, as Franck's noted in its response, *see* Doc. 67, the FDA is currently "requesting comments on approaches for increasing the number of legally-marketed animal drug products, as well as on the use of enforcement discretion for some unapproved animal drug products in certain limited circumstances." 75 Fed.Reg. 79,383 (Dec. 20, 2010); *see also* 76 Fed.Reg. 9584 (Feb. 1, 2011) (extending comment period to April 11, 2011). Although the Request for Comment does not specifically mention compounding, it seems to address both compounded animal drugs and a number of the concerns raised by the 2005 Congressional letters: "For many years, FDA has been aware that a wide variety of animal drug products are being marketed that meet the definition of 'drug' and 'new animal drug' as defined in the FDCA, but are not approved, conditionally approved, or indexed. *Many of these unapproved animal drugs were, and some continue to be, the standard of care in treating animals, and some are essential to protecting animal health and ensuring an adequate food supply.*" 76 Fed.Reg. at 79,383 (providing as examples "injectable vitamins, various topical solutions, shampoos, and liniments, electrolyte and glucose solutions, and antidotes") (emphasis added). Though the extended comment period has expired, *see* 76 Fed.Reg. 9584, the FDA has taken no further action which would impact the Court's resolution of this case.

53 Franck's was a member of a coalition of five pharmacies that filed an amicus brief in support of the plaintiff pharmacies. Franck Dec. ¶ 126.

54 Because its analysis relied in part on FDAMA, the district court addressed whether the non-advertising provisions were severable from the remainder of the amendment and concluded that they were, rendering the remaining provisions of FDAMA still valid. *Id.* at 862–63. The Fifth Circuit ultimately upheld this portion of the district court's holding. *See Med. Ctr.,* 536 F.3d at 404–05.

55 "For example, provisions of the 1962 amendments to the FDCA exempt from registration and inspection requirements licensed 'pharmacies ... which do not ... compound ... drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail.' §§ 360(g)(1), 374(a)(2)(A). As the FDA points out, however,

this reference to compounding cuts another way, as it also suggests Congress's awareness of compounding and its ability to create exceptions for compounding when it chooses to do so." *Id.* at 398, n. 33.

56 By way of example (though this was not mentioned by the Fifth Circuit), AMDUCA does not mention the words "compounding" or "pharmacy," while FDAMA, i.e. 21 U.S.C. § 353a, is *entitled* "Pharmacy Compounding."

57 "[I]f an approval of an application filed under subsection (b) [the new animal drug approval provision] is in effect with respect to a particular use or intended use of a new animal drug, the drug shall not be deemed unsafe for the purposes of paragraph (1) and shall be exempt from the requirements of section 352(f) of this title *with respect to a different use or intended use of the drug,* other than a use in or on animal feed...." 21 U.S.C. § 360b(a)(4) (emphasis added).

58 "If the approval of an application filed under section 355 of this title [the new human drug approval provision] is in effect, the drug under such application shall not be deemed unsafe for purposes of paragraph (1) and shall be exempt from the requirements of section 352(f) of this title *with respect to a use or intended use of the drug in animals* ..." 21 U.S.C. § 360b(a)(5) (emphasis added).

59 The FDA has stated that "[D]efendant's practices of distributing new animal drugs compounded from bulk threatens the approval process that the FDA has instituted and that the statute has mandated so that consumers of drugs can guarantee that they're drugs and guarantee as close to possible that they're safe and effective." Doc. 62 at 7–8; *see also* Doc. 47 at 14 (Court: "[I]s it the government's position that any compounding of bulk materials that is then used for animal medication is a violation of the [FDCA]?" FDA counsel: "That is correct. It is.")

60 Though the FDA notes that its regulations implementing AMDUCA provide that "Nothing in this part shall be construed as permitting compounding from bulk drugs," 21 C.F.R. § 530.13, it rightly does not rely upon that regulation for its authority to *prohibit* the practice. Rather, it argues that AMDUCA cannot be read to *permit* compounding, because the language of § 530.13 demonstrates that "the AMDUCA exemptions are limited to compounding from approved drugs." Doc. 54 at 7.

61 Franck's originally alleged in its Answer that the FDA's enforcement action is arbitrary, capricious, and unconstitutional, but elected not to pursue these defenses at summary judgment, focusing instead on its statutory arguments.

62 The Supreme Court has held—in the human drug context—that a drug is not generally recognized among experts as safe and effective without the adequate and well-controlled studies that would be required for its approval under § 355(d) of the FDCA. *Weinberger v. Hynson, Westcott & Dunning,* 412 U.S. 609, 629–30, 93 S.Ct. 2469, 37 L.Ed.2d 207 (1973); *Med. Ctr.,* 536 F.3d at 394. Franck's raises the argument that, due to the inherent policy differences involved in ensuring the safety and effectiveness of human drugs versus non food-producing animal drugs, veterinarians and pharmacists should be considered "experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs," which would automatically exclude prescription medications compounded within a veterinarian-client-patient relationship from the definition of "new animal drug." However, because § 321(v)(1) does not distinguish between food and non food-producing animals, this argument is a non-starter.

63 Though this portion of the Fifth Circuit's analysis addressed the FDCA's "new drug" definition, it applies equally to the definition of "new animal drug."

64 Accordingly, in the 1992 Guide, the FDA cited to *Algon* and *9/1 Kg. Containers* for their analysis "regarding limitations on sale of unapproved and otherwise unlawful products to licensed practitioners." 1992 Guide at 3. Notably, the FDA has provided no evidence in this case—nor has it alleged—that the bulk ingredients utilized by Franck's are either unlawfully obtained or unapproved.

65 Despite this, the FDA announced in the 1996 and 2003 Guides that "two Federal Appeals Court decisions, [*Algon* and *9/1 Kg. Containers*], affirmed the FDA position that the [FDCA] *does not permit veterinarians to compound unapproved finished drug products from bulk drugs,* unless the finished drug is not a new animal drug. The principle established by the court *applies equally to compounding by pharmacists.*" 1996 Guide at 34,850; 2003 Guide at 3 (emphasis added). This language is noticeably absent from the 2002 Guide.

66 The Third Circuit did in fact consider the question of whether the bulk drug exemption impermissibly intruded on the practice of veterinary medicine in violation of the intent of Congress. *Algon,* 879 F.2d at 1163. Because the record demonstrated that "[t]he only real objection to the government's actions in this case appears to be an economic one," the Third Circuit found that "the FDA's action effecting an increase in cost of drugs to practitioners does not undermine the practice of medicine or treatment decisions of veterinarians." *Id.* at 1165–66. Interestingly, the court mentioned in a footnote that two veterinarians, in an amicus brief, had suggested "a greater impact on their practices if their access to bulk drugs is restricted than they had previously described in their affidavits of record." *Id.* at 1165 n. 6. However, the court did not consider the statements because it was "confined to considering those facts reflected in the record before the district court." *Id.*; *cf. supra* n. 21, 29 (describing importance of compounding from bulk in veterinary practice).

67 *See Algon,* 879 F.2d at 1164 ("The issue of whether the FDA can control the supply of *bulk* ingredients does not implicate the question of whether it can control the *use* of these ingredients in finished-form products") (emphasis in original).

68 The "elephant-in-mouseholes doctrine" recognizes that Congress does not delegate decisions of economic and political significance to an agency in a vague or cryptic fashion; that is, it does not hide elephants in mouseholes. *Gonzales,* 546 U.S. at 267, 126 S.Ct. 904 (citing *Whitman v. American Trucking Assns., Inc.,* 531 U.S. 457, 468, 121 S.Ct. 903, 149 L.Ed.2d 1 (2001); *Brown & Williamson,* 529 U.S. at 160, 120 S.Ct. 1291).

69 The "plain statement rule" requires that Congress speak in clear terms when displacing traditional state regulation of a particular practice. *Gregory v. Ashcroft,* 501 U.S. 452, 460–61, 111 S.Ct. 2395, 115 L.Ed.2d 410 (1991).

70 The "rule of lenity" requires that when a statute carries criminal penalties, any ambiguities must be interpreted in the defendant's favor to avoid "prohibit[ing] more conduct or punish[ing] more severely than Congress intended." *United States v. Wright,* 607 F.3d 708, 717 (11th Cir.2010) (Pryor, J., concurring).

71 *See Med. Ctr.,* 451 F.Supp.2d at 858, 864 ("[C]ompound drugs are implicitly exempt from the [FDCA's] new drug definitions ... [T]his Court finds that if compounding is a legal activity, then *any drugs created through the compounding process must be exempt from the new drug definitions found in the [FDCA]* ") (emphasis added).

72 Notably, because of the district court's ruling, the Fifth Circuit was faced with the argument that compounded drugs were entirely beyond the scope of the FDCA's new *human* drug provisions, a position that could not be squared with the plain language of the statute as amended by FDAMA.

73 *Cf. supra* n. 20, 27, 38.

74 In *Medical Center,* the pharmacies had taken the opposite per se position that all pharmacy compounding was legal.

75 *See* Doc. 47 at 16. Specifically, while FDAMA permits compounding of human drugs from bulk substances under certain circumstances, the practice is entirely prohibited for animals—except for nine listed exceptions—by the 2003 Guide. *See supra* at 1227–29.

76 This is not altogether surprising, as the Fifth Circuit had no occasion to do so given the posture of the case as framed by the district court. However, it is apparent from a review of the Fifth Circuit's opinion that the Court analyzed the issue of compounding human drugs far more thoroughly than it did compounding animal drugs. Of specific note, the Court did not discuss any of the policy differences between the 2002 and 2003 Guides, and its analysis of AMDUCA as an analog to FDAMA is, with due respect, unpersuasive. The FDA apparently shares this view; while it certainly likes the outcome reached by the Fifth Circuit, nowhere in its briefing or argument does the FDA embrace that court's statutory construction, which relied heavily upon AMDUCA. This may represent a subtle concession that the Fifth Circuit's analysis of the "new animal drug" issue was less than watertight.

77 An agency's interpretation of its own ambiguous regulation promulgated pursuant to a congressional grant of authority is "controlling unless plainly erroneous or inconsistent with the regulation." *Auer v. Robbins,* 519 U.S. 452, 461, 117 S.Ct. 905, 137 L.Ed.2d 79 (1997) (quotation omitted).

78 This reasoning became the foundation for the Court's invocation of the elephant-in-mouseholes doctrine in *American Trucking,* 531 U.S. at 468, 121 S.Ct. 903.

79 Franck's also finds support in recent Eleventh Circuit case law. *See Durr,* 638 F.3d at 1349 (describing circumstances where courts may reach results inconsistent with the plain language of a statute by looking to the provisions of the whole law, and to its policy).

80 *See Algon,* 879 F.2d at 1158 ("The statutory definition of a 'new drug' ... does not exempt drugs that are compounded by veterinarians"); *cf. Prof'ls and Patients,* 56 F.3d at 593 n. 3 ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug, adulteration, or misbranding provisions, *the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding"*) (emphasis added).

81 The Fifth Circuit in *Medical Center* cited these entries from the FDCA's legislative history:

> The President of the American Pharmaceutical Association told a subcommittee of the Senate Committee on Commerce the following:
>
> > 'Regulations governing ... the practice of pharmacy by pharmacists are very strict, but the privileges of unlicensed persons operating outside of pharmacies are so extensive that the public enjoys little protection in the matter of sales of packaged medicines.' Foods, Drugs, and Cosmetics: Hearings Before a Subcomm. of the Comm. on Commerce, 74th Cong. 100, 102 (1935) (statement of Robert P. Fischelis, President, American Pharmaceutical Ass'n) (quoting survey by committee on costs of medical care).
>
> In a similar vein, Representative Coffee made remarks to the House, approvingly quoting the Secretary of Agriculture:
>
> > 'Pharmacists are licensed to compound and dispense drugs. Electricians, plumbers, and steam engineers pursue their respective trades under license. But there is no such control to prevent incompetent drug manufacturers from

marketing any kind of lethal poison.' Extension of Remarks of Rep. John M. Coffee, 83 Cong. Rec. 2279, 2279 (June 1, 1938) (quoting Henry A. Wallace, Secretary of Agriculture).

Med. Ctr., 536 F.3d at 397 (footnotes converted to text).

82 *See* Florida Pharmacy Act, Fla. Stat. §§ 465.001 *et seq.* (creating the Florida Board of Pharmacy and conferring upon the Board the duty to regulate the practice of pharmacy within the state); *id.* § 465.003(13) (" 'Practice of the profession of pharmacy' *includes compounding,* dispensing, and consulting concerning contents, therapeutic values, and uses of any medicinal drug ....") (emphasis added); Fla. Admin. Code Ann. 64B16–27.700(1) ("Compounding includes: (a) The preparation of drugs or devices in anticipation of prescriptions based on routine, regularly observed prescribing patterns. (b) The preparation pursuant to a prescription of drugs or devices which are not commercially available. (c) The preparation of commercially available products from bulk when the prescribing practitioner has prescribed the compounded product on a per prescription basis and the patient has been made aware that the compounded product will be prepared by the pharmacist ....").

83 *See* Dinah G. Jordan, "Pharmacist compounding vs. veterinarian compounding: Similarities and differences," Journal of the American Veterinary Medical Association (July 15, 1995), at 258 ("There must exist a bona fide prescriber/pharmacist/patient relationship to distinguish compounding from manufacturing. Manufactured products are for resale; compounded products are not .... Herein lies the basic difference between compounding and manufacturing").

84 *See* Bradshaw Dec. ¶ 44 ("Drug manufacturing generally is understood to consist of the mass commercialization of proprietary or patented drugs in standard formulations and dosages for a large-scale market. Drug manufacturers routinely produce batches consisting of millions of dosage units, such as tablets or capsules, for resale utilizing many personnel and large-scale manufacturing equipment. These drug products are distributed through the normal channels of interstate commerce to individuals unknown to the manufacturing company. Manufacturers are not required to, and do not, provide oversight of individual patients. Federal regulation of large-scale commercial manufacturing is intended to prevent the production of large quantities of ineffective or dangerous manufactured drugs that then are introduced into interstate commerce").

85 In *Western States,* the Supreme Court suggested several means to draw "a line between compounding and large-scale manufacturing" which would be sufficient to "prevent compounding from occurring on such a scale as to undermine the new drug approval process." *W. States,* 535 U.S. at 372–73, 122 S.Ct. 1497; *supra* n. 45.

86 Or, in the parlance of the 1996 Guide, the "legitimate practice" of pharmacists and veterinarians.

87 *See, e.g.,* CVM Update, "CVM Working to Address Concerns about Supplies of Pergolide for Horses," May 11, 2007, *available at* http://www. fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048035.htm ("FDA is working with the sponsors of the approved products and all other interested parties to ensure that pergolide remains available to treat Cushing's Syndrome in horses until a new animal drug application is approved for that use. This includes trying to make the approved product available through veterinary distribution channels and exercising enforcement discretion as appropriate over the pharmacy compounding of pergolide. Bulk substance used for pharmacy compounding should be labeled for 'animal use only.' All pharmacy compounding must be done under a valid veterinary prescription to treat an affected horse").

88 "In developing my independent compounding pharmacy, I have relied on the fact that pharmacy compounding practices have long and traditionally been regulated by the states." *Id.*

89 The FDA claims this cuts another way, namely that pharmacists such as Franck's (which has been compounding since 1983) have been on notice of the agency's asserted authority in this area—and the potential for regulatory enforcement—since the days of *Algon* and *9/1 Kg. Containers. But cf. Northwest Tissue Center v. Shalala,* 1 F.3d 522, 533 (7th Cir.1993) ("Suppose an agency charged with regulating the nation's highways promulgates regulations requiring 'all vehicles' to conform to certain safety standards. For five years the agency enforces these standards only against automobiles of various types. Then it publishes a notice in the Federal Register announcing that the regulations also apply to bicycles. The dictionary definition of vehicle ('A device, such as a car or sled, for carrying passengers, goods, or equipment; conveyance ....') reasonably encompasses bicycle as a permissible interpretation. Nevertheless, it seems silly to suggest that the nation's bicyclists would have been 'on notice' at the time the regulations were promulgated that the agency's standards applied to their bikes.")

90 It is the FDA's position that its broad discretionary authority is bridled only by its "responsibility to choose its enforcement actions wisely and under some merit and under some thoughtful consideration." (Doc. 47 at 23.)

91 The Fifth Circuit stated: "[E]ven if compounded drugs are effectively made unlawful by the 'new drug' definition and approval requirements, pharmacists still could continue compounding to the extent allowed by the FDA's enforcement discretion. The FDA did not enforce the 'new drug' requirement against traditional compounding for decades, and the

agency's Compliance Policy Guide declared only a limited intention to conduct future enforcement in cases in which compounding looks more like disguised manufacturing." *Med. Ctr.,* 536 F.3d at 399.

92 *See, e.g., supra* n. 21 and accompanying text; *supra* n. 29; Davidson Dec. Ex. 13, "Veterinary Drug Compounding in the US, July 2003," prepared by Brakke Consulting, Inc., at 5–6 ("There are hundreds of approved animal drugs on the market in the US, but the cost of obtaining FDA–CVM approval for a non-food animal drug is estimated at around $15–20 million and 5 years .... Because the anticipated sales volume of most veterinary drugs is far below the $100 million per year mark, and research and development budgets are shrinking, the number of new chemical entities approved by the FDA–CVM has been declining for some time.... All this means there are limited products at a veterinarian's disposal to treat his or her patients.").

93 *Cf., e.g., Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.,* 463 U.S. 29, 41–42, 103 S.Ct. 2856, 77 L.Ed.2d 443 (1983) (holding that "[a] settled course of behavior embodies the agency's informed judgment that, by pursuing that course, it will carry out the policies committed to it by Congress") (internal quotation omitted); *Thomas Jefferson University v. Shalala,* 512 U.S. 504, 524 n. 3, 114 S.Ct. 2381, 129 L.Ed.2d 405 (1994) (Thomas, J., dissenting) ("[A]gency conduct, no less than express statements, can effect a construction of statutes or regulations").

94 The FDA argues that the federal-state distinction is a red herring because "the FDCA explicitly provides the FDA with authority to regulate drugs that travel through interstate commerce[, and f]or that reason alone the Defendants' drugs are subject to federal oversight." Doc. 60 at 14 (internal citation omitted). This misstates the question. The plain statement rule is implicated because the FDA claims that its authority to regulate within a traditionally state-regulated arena *is derived from a seventy-year old statute which is silent on the topic and which has never before been applied to such conduct.* For the same reasons, the FDA's reliance upon *Sullivan,* 332 U.S. at 692–93, 68 S.Ct. 331, as "long ago reject[ing] the proposition that traditional state authority limits the FDCA," Doc. 60 at 14–15, is misplaced.

95 The FDA cites to *Kordel v. United States,* 335 U.S. 345, 348–49, 69 S.Ct. 106, 93 L.Ed. 52 (1948) as "definitively reject[ing]" application of the rule of lenity to the FDCA. This appears to be an overly broad interpretation of *Kordel,* and the FDA has not otherwise demonstrated that case's applicability here.

96 Had the FDA done what it said it would do or, even better, gone through formal rule-making, it might have been able to develop criteria for determining whether a large, interstate compounding pharmacy such as Franck's is engaging in impermissible manufacturing or permissible, traditional compounding. *See W. States,* 535 U.S. at 372–73, 122 S.Ct. 1497 (suggesting such criteria); *supra* n. 45, 83. Though it is not my place to say so, FDA could still choose to follow this alternative course. *See supra* n. 52 (FDA seeking comments in related area). Or, as it did in the case of tobacco, *see* Family Smoking Prevention and Tobacco Control Act of 2009, Pub.L. 111–31 (HR 1256) (2009), it could ask Congress for the explicit authority to regulate this practice.

97 Because of this ruling, the Court need not reach other issues raised by the parties, including the standards governing the Court's decision whether to grant the FDA injunctive relief.

536 F.3d 383
United States Court of Appeals,
Fifth Circuit.

MEDICAL CENTER PHARMACY; Applied Pharmacy; College Pharmacy; Med Shop Total Care Pharmacy; Pet Health Pharmacy Incorporated; Plum Creek Pharmaceuticals Incorporated; Premier Pharmacy; University Compounding Pharmacy; Veterinary Pharmacies of America; Women's International Pharmacy Incorporated, Plaintiffs–Appellees,
v.
Michael B. MUKASEY, U.S. Attorney General, United States Department of Justice, in His Official Capacity; Michael O. Leavitt, Secretary, Department of Health and Human Services, in His Official Capacity; Andrew C. von Eschenbach, Commissioner of the United States Food and Drug Administration, in His Official Capacity, Defendants–Appellants.

No. 06–51583.
|
July 18, 2008.

Synopsis

Background: Group of ten state-licensed pharmacies that specialized in compounding prescription drugs for humans and non-food animals filed lawsuit challenging the authority of the Food and Drug Administration (FDA) to regulate compounded drugs and to inspect state-licensed retail pharmacies under the Food, Drug and Cosmetic Act. The parties filed motions for summary judgment. The United States District Court for the Western District of Texas, Robert A. Junell, J., 451 F.Supp.2d 854, granted motions in part and denied them in part, and the FDA appealed.

Holdings: The Court of Appeals, Jerry E. Smith, Circuit Judge, held that:

[1] compounded drug, to extent that compounding process had changed composition of drug previously approved by the FDA, qualified as "new drug," of a kind potentially subject to new-drug-approval requirements of the Federal Food, Drug and Cosmetic Act (FDCA);

[2] provisions of the Food and Drug Administration Modernization Act (FDAMA), other than advertising provisions that were struck down as unconstitutional by the United States Supreme Court, were severable from these unconstitutional provisions; and

[3] drug products compounded in bulk for animal use by pharmacists and veterinarians were "new animal drugs," that were subject to the Federal Food, Drug and Cosmetic Act's (FDCA's) unsafe, adulteration and misbranding requirements, unless these compounded drugs were exempt under the FDCA's Animal Medicinal Drug Use Clarification Act (AMDUCA).

Vacated and remanded.

West Headnotes (27)

[1] **Federal Courts**
Failure to mention or inadequacy of treatment of error in appellate briefs

Food and Drug Administration (FDA), by arguing on appeal that Court of Appeals did not need to address severability of other provisions of the Food and Drug Administration Modernization Act (FDAMA) from provision that had been found unconstitutional, did not waive right to challenge severability holding, where the FDA stated its position on severability in body of its appellate brief, made argument, albeit an austere one, in defense of its position, and cited relevant authority. Federal Food, Drug, and Cosmetic Act, § 503A, 21 U.S.C.A. § 353a.

1 Cases that cite this headnote

[2] **Federal Courts**
Statutes, regulations, and ordinances, questions concerning in general
Federal Courts
Summary judgment

Court of Appeals reviews *de novo* district

court's grant of summary judgment and its conclusions on questions of statutory interpretation.

Cases that cite this headnote

[3] **Administrative Law and Procedure**
Plain, literal, or clear meaning; ambiguity
Administrative Law and Procedure
Permissible or reasonable construction

On *Chevron* review of agency's interpretation of statute that it is charged with administering, the Court of Appeals employs two-step inquiry, under which it first asks whether Congress has directly spoken to the precise question at issue, such that Court must give effect to unambiguously expressed intent of Congress, and only if Congress has not directly addressed the precise question at issue does it then defer to any permissible construction of statute by agency.

7 Cases that cite this headnote

[4] **Administrative Law and Procedure**
Erroneous construction; conflict with statute

On *Chevron* review of agency's construction of statute that it has found to be ambiguous, the Court of Appeals will reverse agency's decision only if it is arbitrary, capricious, or manifestly contrary to statute.

1 Cases that cite this headnote

[5] **Health**
New drugs

Compounded drug, to extent that compounding process has changed composition of a drug previously approved by the Food and Drug Administration (FDA), e.g., by mixing or combining it with something else to create a different substance or by creating special dosage or delivery forms of the previously approved drug that are inconsistent with drug's labeling, qualifies as "new drug," of a kind potentially subject to new-drug-approval requirements of the Federal Food, Drug and Cosmetic Act (FDCA), unless this compounded drug comes within "safe harbor" created by the Food and Drug Administration Modernization Act (FDAMA) for compounded drugs that comply with conditions explicitly delineated in the FDAMA. Federal Food, Drug, and Cosmetic Act, §§ 201(p)(1), 503A, 21 U.S.C.A. § 321(p)(1), 353a.

4 Cases that cite this headnote

[6] **Statutes**
Language and intent, will, purpose, or policy

There is no better or more authoritative expression of Congressional intent in enacting statute than statutory text.

2 Cases that cite this headnote

[7] **Statutes**
Absence of Ambiguity; Application of Clear or Unambiguous Statute or Language
Statutes
Plain language; plain, ordinary, common, or literal meaning
Statutes
Statutory scheme in general

In all statutory construction cases, the Court of Appeals begins with language of statute and, if statutory language is unambiguous and statutory scheme is coherent and consistent, then that is usually where the Court ends.

1 Cases that cite this headnote

[8] **Health**

New drugs

Any drug, the composition of which has not already been approved by the Food and Drug Administration (FDA) for use in accordance with its labeling, qualifies as "new drug," within meaning of the Federal Food, Drug and Cosmetic Act (FDCA). Federal Food, Drug, and Cosmetic Act, § 201(p)(1), 21 U.S.C.A. § 321(p)(1).

Cases that cite this headnote

[9] **Health**
New drugs

Definition of "new drug" under the Federal Food, Drug and Cosmetic Act (FDCA) focuses on drug's composition and use, rather than on process by which drug was created, such that it is immaterial whether drug was created by manufacturing or by compounding. Federal Food, Drug, and Cosmetic Act, § 201(p)(1), 21 U.S.C.A. § 321(p)(1).

2 Cases that cite this headnote

[10] **Statutes**
Express mention and implied exclusion; expressio unius est exclusio alterius

When Congress creates specific exceptions to a broadly applicable provision, proper inference is that Congress considered issue of exceptions and, in the end, limited statutory exceptions to the ones set forth in statute.

1 Cases that cite this headnote

[11] **Statutes**
What constitutes ambiguity; how determined

Upon discovering that statute's plain text is in tension with its supposed purpose, court usually concludes that Congress has spoken ambiguously.

1 Cases that cite this headnote

[12] **Administrative Law and Procedure**
Trade or business
Health
Judicial review or intervention

To persuade the Court of Appeals to reject the Food and Drug Administration's (FDA's) interpretation of the term "new drug," as used in the Federal Food, Drug and Cosmetic Act (FDCA), as being broad enough to include compounded drugs produced by pharmacies, pharmacies had to do more than demonstrate that tension that existed between plain text of definition of "new drug" in the FDCA and the FDCA's stated purpose was sufficient to create ambiguity; pharmacies could avoid *Chevron* deference only by establishing that Congressional intent was in fact not ambiguous, i.e., that statute's purpose was so clear and compelling, despite tension with its plain text, that it left no doubt that Congress' intent was contrary to the FDA's interpretation of term. Federal Food, Drug, and Cosmetic Act, § 201(p)(1), 21 U.S.C.A. § 321(p)(1).

2 Cases that cite this headnote

[13] **Health**
New drugs

Construing term "new drug," as used in the Federal Food, Drug and Cosmetic Act (FDCA), as broad enough to include compounded drugs, so as to give the Food and Drug Administration (FDA) authority over drug compounding, would not necessarily lead to result that was so bizarre that Congress could not have intended it, at least not given the FDA's statutorily-authorized enforcement discretion and its demonstrated willingness to accommodate continued existence of traditional compounding; accordingly, ubiquity of pharmacy compounding at time of

the FDCA's enactment was insufficient basis for applying the elephant-in-mousehole doctrine to construe "new drugs" as not including compounded drugs. Federal Food, Drug, and Cosmetic Act, § 201(p)(1), 21 U.S.C.A. § 321(p)(1).

5 Cases that cite this headnote

[14] **Statutes**
Debates, speeches, and floor statements

Floor statements from individual senators cannot alter clear and unambiguous language of statute, and in interpreting statute, there is no reason for court to give greater weight to views of individual senators than to collective votes of both Houses, which are memorialized in unambiguous statutory text.

Cases that cite this headnote

[15] **Statutes**
General and specific statutes
Statutes
Earlier and later statutes

Over time, subsequent acts can shape or focus a statute's range of plausible meanings, particularly when scope of earlier statute is broad but the subsequent statutes more specifically address topic at hand.

Cases that cite this headnote

[16] **Statutes**
Legislative Construction

Where a subsequent Congress has not enacted a valid amendment, intent of prior Congress that enacted the original statute is best guide to meaning of statute that it promulgated.

Cases that cite this headnote

[17] **Statutes**
Effect of Total Invalidity
Statutes
Effect of Partial Invalidity; Severability

If act of amendment is invalid, e.g., because its unconstitutional portions cannot be severed, then act is void *ab initio*, and it is as though Congress never enacted it at all.

Cases that cite this headnote

[18] **Statutes**
Environment and health

Provisions of the Food and Drug Administration Modernization Act (FDAMA), other than advertising provisions that were struck down as unconstitutional by the United States Supreme Court, were severable from these unconstitutional provisions, such that the Court of Appeals could look to these valid provisions for assistance in assessing whether the Food and Drug Administration (FDA) permissibly interpreted the term "new drug," as used in the Federal Food, Drug and Cosmetic Act (FDCA), as being broad enough to include compounded drugs; neither the FDAMA's text nor its inconclusive legislative history amounted to "strong evidence," sufficient to overcome presumption of severability arising from presence of severability clause in act that the FDAMA amended. Federal Food, Drug, and Cosmetic Act, §§ 201(p)(1), 503A, 21 U.S.C.A. § 321(p)(1), 353a.

1 Cases that cite this headnote

[19] **Statutes**
Effect of Partial Invalidity; Severability

Unless it is evident that legislature would not

have enacted those provisions which are within its power, independently of that which is not, invalid part of enactment may be severed, if what remains is fully operative as law.

Cases that cite this headnote

[20] **Statutes**
Effect of Partial Invalidity; Severability

Relevant inquiry in evaluating severability of statute, one of whose parts has been found to be invalid, is whether the severed statute will function in manner consistent with intent of Congress.

Cases that cite this headnote

[21] **Statutes**
Effect of severability clause

Crucial clue to whether Congress intended for statute to be severable is Congress' decision to include express severability provision in statute.

Cases that cite this headnote

[22] **Statutes**
Effect of severability clause

When Congress, while not including express severability provision in one of its enactments, nevertheless enacts it as amendment to act that contains such a provision, strong presumption arises that Congress intended for provisions of amendment to be severable, a presumption which may be overcome only by strong evidence that Congress would not have enacted amendment without the provisions found to be invalid.

Cases that cite this headnote

[23] **Statutes**
Effect of Partial Invalidity; Severability

When statute's invalidated provision is one of series of conditions, each of which is designed to promote common goal, courts deem statute to be severable.

Cases that cite this headnote

[24] **Statutes**
Superfluousness

Cardinal principle of statutory construction is that statute should be construed such that no clause, sentence or word shall be superfluous, void or insignificant.

Cases that cite this headnote

[25] **Health**
New drugs

Compounded drugs, to extent that compounding process had changed composition of drugs previously approved by the Food and Drug Administration (FDA), e.g., by mixing or combining them with something else to create different substances, were exempt from new-drug-approval requirements of the Federal Food, Drug and Cosmetic Act (FDCA), if and only if these compounded drugs satisfied requirements of "safe harbor" created by the Food and Drug Administration Modernization Act (FDAMA). Federal Food, Drug, and Cosmetic Act, §§ 201(p)(1), 503A, 21 U.S.C.A. §§ 321(p)(1), 353a.

5 Cases that cite this headnote

[26] **Health**
Animal drugs

Drug products compounded in bulk for animal use by pharmacists and veterinarians were "new animal drugs," that were subject to the Federal Food, Drug and Cosmetic Act's (FDCA's) unsafe, adulteration and misbranding requirements, unless these compounded drugs were exempt under the FDCA's Animal Medicinal Drug Use Clarification Act (AMDUCA) provisions. Federal Food, Drug, and Cosmetic Act, §§ 201(v)(1), 512(a)(4, 5), 21 U.S.C.A. §§ 321(v)(1), 360b(a)(4, 5).

2 Cases that cite this headnote

[27] **Health**
Animal drugs

Any animal drug, the composition of which has not already been approved by the Food and Drug Administration (FDA), constitutes "new animal drug," within meaning of the Federal Food, Drug and Cosmetic Act (FDCA). Federal Food, Drug, and Cosmetic Act, § 201(v)(1), 21 U.S.C.A. § 321(v)(1).

Cases that cite this headnote

West Codenotes

Recognized as Unconstitutional
21 U.S.C.A. § 353a

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Appeal from the United States District Court for the Western District of Texas.

Before HIGGINBOTHAM, DAVIS and SMITH, Circuit Judges.

Opinion

JERRY E. SMITH, Circuit Judge:

In this appeal we clarify the extent to which the Federal Food Drug and Cosmetic Act of 1938 (the "FDCA" or the "Act"), 21 U.S.C. §§ 301–397, permits the Food and Drug Administration ("FDA") to regulate a common practice of pharmacies known as "compounding." Ten pharmacies specializing in compounding prescription drugs for human and animal use (the "Pharmacies") sued various federal agencies (collectively, the "FDA") for declaratory and injunctive relief permitting them to continue compounding drugs without obtaining the FDA approval required for "new drugs" under the Act, 21 U.S.C. § 321(p) and (v). Concluding that the FDCA, as amended, permits compounded drugs to avoid the new drug approval process but that the exception applies only in certain statutorily-delimited circumstances, we vacate and remand.

I.

A.

Drug compounding is the process by which a pharmacist combines or alters drug ingredients according to a doctor's prescription to create a medication to meet the unique needs of an individual human or animal patient.[1]

Compounding is "typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product." *W. States*, 535 U.S. at 361, 122 S.Ct. 1497. According to the American Pharmacists Association, as *amici*, pharmacists compound patient-specific medication for a variety of medical purposes, including cancer treatment, where dosages must be calibrated to a "patient's body size, the type of ***388** cancer, the size and type of tumor, and the clinical condition of the patient;" pediatric treatment, where available drug dosages must be modified and diluted for use in children; elderly hospice care, where patients who no longer benefit from curative treatment use compounded dosages therapeutically to "establish optimal pain and symptom control;" and hospital stays, where "intravenous admixtures" must be highly individualized to allow administration of drugs "not suitable for other routes of administration."

Compounding has deep roots; it "is a traditional component of the practice of pharmacy and is taught as part of the standard curriculum at most pharmacy schools." *Id.* (citation omitted). Since 1820, pharmacists have relied on compounding instructions contained in the *U.S. Pharmacopeia*,[2] an independent compendium of drug standards whose authority is recognized by reference in federal law.[3] "Many States specifically regulate compounding practices as part of their regulation of pharmacies. Some require all licensed pharmacies to offer compounding services." *Id.* (citations omitted).

In 1938, Congress enacted the FDCA to regulate drug manufacturing, marketing, and distribution. The Act empowers the FDA to require approval of any "new drug,"[4] which the Act defines as "[a]ny drug (except a new animal drug ...) the composition of which is such that such drug is not generally recognized ... as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof."[5] The Act likewise requires approval of "new animal drugs"[6] and defines "new animal drug" in similar terms.[7]

To be deemed "safe and effective" and thereby obtain FDA approval, a new drug must undergo an extensive application and approval process.[8] Under the FDCA, an FDA finding of "safe and effective" must be based on "substantial evidence" of expert consensus.[9] The "test is rigorous,"[10] ***389** requiring expensive and time-consuming clinical trials estimated by some to cost more than $800 million per drug.[11]

A question emerged from Congress's enactment of the FDCA: When a pharmacist creates a compounded medication to suit an individual patient, does the resulting creation constitute a "new drug" requiring FDA approval? If each individualized drug product produced through compounding required FDA approval, few would undergo the costly and arduous approval process. And the lack of approval would in turn make nearly all compounding unlawful under the FDCA. Although the question whether compounded drugs are "new drugs" was not before it, the Court has noted in *dictum* that

> it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs.

Id. at 369–70.[12]

For roughly fifty years following the FDCA's enactment, the compounding question lay dormant, without dispute and without answer. The FDA did not seek to enforce "new drug" approval requirements against compounding pharmacists but instead left regulation of compounding to the states, and pharmacists continued to compound drugs without seeking FDA approval.[13] In the early 1990's, however, the FDA became concerned that some pharmacies were purchasing bulk quantities of drug products, "compounding" them into specific drug products before receiving individual prescriptions, and marketing those drugs to doctors and patients. Although the agency had long refrained from regulating pharmacist compounding, it believed that pharmacies engaging in large-scale bulk compounding were effectively manufacturing drugs under the guise of compounding them—using the FDA's traditional ***390** lenience toward compounding as an end-run around the new drug approval, adulteration, and misbranding provisions of the FDCA.[14]

Ostensibly to prevent this end-run around its regulation of drug manufacturing, the FDA in 1992 promulgated Compliance Policy Guide No. 7132.16 (Mar.1992) ("CPG 7132.16"), deemed by this circuit in *Professionals & Patients*, 56 F.3d at 595–602, to be a valid agency rule under the Administrative Procedures Act. The Guide explained that "while retail pharmacies ... are exempted

from certain requirements of the [FDCA], they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions." CPG 7132.16, at 1.

Although asserting its expansive authority under the FDCA to require formal approval of all compounded drugs, the FDA declared its intention "generally [to] continue to defer to state and local officials regulation of the day-to-day practice of retail pharmacy and related activities." *Id.* at 4. Nevertheless, the FDA warned that it "may, in the exercise of its enforcement discretion, initiate federal enforcement actions against entities and responsible persons when the scope and nature of a pharmacy's activity raises the kind of concerns normally associated with a manufacturer." *Id.* The FDA went on to list nine non-exhaustive factors it would consider in exercising its enforcement discretion against certain kinds of manufacturing-as-compounding considered to be hazardous to public health.[15]

A few years later, in a move the Pharmacies call a reaction to the FDA's 1992 policy and the FDA characterizes as a confirmation of it, Congress amended the FDCA by enacting the Food And Drug Modernization Act of 1997 ("FDAMA"), Pub.L. No. 105–115, 111 Stat. 2296 (codified as amended at 21 U.S.C. § 353a (2000)). Explicitly addressing "pharmacy compounding," FDAMA sought to permit pharmacy compounding by exempting compounded drugs from the FDCA's new drug approval, adulteration, and misbranding provisions, but FDAMA simultaneously conditioned the exemption on compliance with a number of restrictions on compounding practices and pharmacy advertising. Much like the FDA's 1992 policy, FDAMA created a safe harbor ***391** from the FDCA's new drug approval requirements so long as a compounding pharmacist observed a number of requirements designed to ensure the pharmacist was engaged in traditional compounding rather than disguised manufacturing.[16]

Although FDAMA did not cover animal drugs, Congress also amended the FDCA by enacting the Animal Medicinal Drug Use Clarification Act of 1994 ("AMDUCA"), Pub.L. No. 103–396, 108 Stat. 4153 (codified as amended at § 360b(a)(4), (5)). In a similar manner as FDAMA, the AMDUCA amended the FDCA by exempting some extra-label uses of animal drugs from the new drug approval process while restricting this exemption to certain narrow circumstances.

Shortly after passage of FDAMA, however, trouble arose. In 2002, in *Western States*, 535 U.S. at 368–77, 122 S.Ct. 1497, the Court invalidated the advertising-related provisions of FDAMA, affirming the Ninth Circuit's holding that those portions were unconstitutional restrictions on commercial speech. Although the Ninth Circuit had deemed FDAMA non-severable and therefore had invalidated FDAMA in its entirety, *W. States Med. Ctr. v. Shalala*, 238 F.3d 1090, 1096–98 (9th Cir.2001), the Supreme Court declined to address the validity of the remaining non-advertising portions of FDAMA, because the parties had not appealed the severability issue. The Court explained, "Petitioners challenged only the Court of Appeals' constitutional holding in their petition for certiorari, and respondents did not file a cross-petition. We therefore address only the constitutional question, having no occasion to review the Court of Appeals' severability determination." *W. States*, 535 U.S. at 360, 122 S.Ct. 1497.

After the Court invalidated the advertising-related portions of FDAMA, the FDA issued revised Compliance Policy Guides addressing the compounding of human and animal drugs.[17] Observing the Ninth Circuit's severability holding, the agency took the position that "all of [FDAMA] is now invalid." CPG 460.200, at 2. Like their 1992 forebearer, the new Guides assert that compounded human and animal drugs are not exempt from the FDCA's new drug approval, adulteration, or misbranding provisions. But the Guides again assure pharmacists that the FDA will use its enforcement discretion against compounding only where a pharmacy's activities raise the kinds of concerns normally associated with manufacturing. And again, the Guides list factors the FDA will use in determining whether to bring enforcement actions.[18]

***392** B.

The Pharmacies sued for declaratory and injunctive relief, challenging the authority of the FDA to regulate compounded drugs under the FDCA. They sought four principal declaratory judgments:[19] first, that compounded drugs are not "new drugs" or "new animal drugs" under § 321(p)(1) and (v)(1), and on this basis, that they are not subject to the requirements and prohibitions imposed by the FDCA on such drugs; second, that the FDCA permits pharmacists to compound drugs from bulk ingredients for non-food animals; third, that the Pharmacies' compliance with 21 U.S.C. § 374(a)(2)(A) makes them exempt from the heightened "records inspection" authorized by § 374(a)(1); and fourth, that CPG 608.400 violates the Administrative Procedures Act.

The district court granted in part and denied in part the

motions for summary judgment. *Med. Ctr. Pharmacy v. Gonzales*, 451 F.Supp.2d 854 (W.D.Tex.2006). The court granted the Pharmacies' request for declaratory judgment regarding the "records inspection" provision and denied their prayer regarding the Administrative Procedures Act. The court also granted the Pharmacies' request for declaratory judgment regarding compounding from bulk ingredients for non-food animals. The court held, "Drugs compounded from legal bulk ingredients [for non-food animals] do not violate the [FDCA's] unsafe, adulterated or misbranded provisions." *Id.* at 868.

Addressing whether compounded drugs are "new drugs" or "new animal drugs," the court first turned its attention to FDAMA. The court observed that "when enacted, [FDAMA] exempted compounded drugs from the FDA's drug approval process, provided that drug compounders complied with various restrictions." *Id.* at 861. The court therefore found it necessary to address, *sua sponte*, whether FDAMA is non-severable and thus rendered void by the Supreme Court's invalidation of FDAMA's advertising provision. The district court held, "The offending [advertising] portions of § 353a [i.e., FDAMA] are severed and the remainder of the statute remains in full effect." *Id.* at 863.

The district court then reasoned that "the remaining provisions of [FDAMA] demonstrate that Congress intended to declare that compounding is an approved and legal practice." *Id.* Somewhat curiously, in light of its earlier acknowledgment of FDAMA's "various restrictions," the court fashioned a blanket "implicit exemption" from the FDCA's "new drug" definitions that appears to exempt pharmacy compounders regardless of whether they comply with FDAMA's specific restrictions:

> The existence of the remaining portions of the [FDAMA] permit pharmacies to compound drugs. Because pharmacies are permitted to compound, this Court finds that *any drugs* created by the compounding process are authorized under § 353a and are therefore *implicitly exempt* from the new drug approval process and the definitions found in 21 U.S.C. § 321(p)(1) and (v)(1).

Id. (emphasis added).[20] The court reiterated, "In conclusion, this Court finds that ***393** compounded drugs, when created for an individual patient pursuant to a prescription from a licensed practitioner, are implicitly exempt from the new drug definitions contained in 21 U.S.C. §§ 321(p)(1) and (v)(1)." *Id.* at 865.

The FDA appeals the holding that compounded drugs are "implicitly exempt" from the "new drug" and "new animal drug" definitions. The agency also appeals the holding that drugs compounded from bulk ingredients for non-food animals do not violate the FDCA's unsafe, adulteration, or misbranding provisions. Neither party appeals the holdings regarding "records inspection" and the Administrative Procedures Act.

[1] In their briefing on appeal, both sides argue that we need not address severability to decide whether the FDCA's "new drug" definitions exempt compounded drugs. For reasons explained below, we disagree and, having found it necessary to reach the severability question, we requested supplemental briefing on that issue.[21]

II.

[2] [3] [4] We review *de novo* summary judgments and questions of statutory interpretation. *Southwestern Bell Tel., L.P. v. Pub. Util. Comm'n*, 467 F.3d 418, 421 (5th Cir.2006). Under *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 104 S.Ct. 2778, 81 L.Ed.2d 694 (1984), we apply a two-step inquiry to an agency's interpretation of its statutory authority. First, we ask "whether Congress has directly spoken to the precise question at issue," *id.* at 842, 104 S.Ct. 2778, and if so, we "must give effect to the unambiguously expressed intent of Congress," *id.* at 843, 104 S.Ct. 2778. Second, if "Congress has not directly addressed the precise question at issue," the statutory provision is ambiguous and the court must defer to any "permissible construction of the statute" by the agency. *Id.* Under *Chevron*'s second step, we "reverse [an] agency's decision only if it [is] 'arbitrary, capricious, or manifestly contrary to the statute.' " *Tex. Coal. of Cities for Util. Issues v. FCC*, 324 F.3d 802, 807 (5th Cir.2003) (quoting *Chevron*, 467 U.S. at 844, 104 S.Ct. 2778).

III.

[5] Agreeing with the Pharmacies, the district court held that compounded drugs are not "new drugs" within the meaning of § 321(p)(1) of the FDCA, and on that basis, the court held that compounded drugs are uniformly exempt from the FDCA's ***394** new drug approval

requirements. The FDA argues that compounded drugs *are* "new drugs" and consequently must satisfy the new drug approval requirements. We disagree with the district court and agree with the FDA as to whether compounded drugs are "new drugs." We disagree with both sides, however, regarding the implications of that conclusion.

Though compounded drugs are "new drugs," they are neither *uniformly* exempt from the new drug approval requirements nor *uniformly* subject to them. Properly construed, the statutory scheme as amended by FDAMA creates a *limited* exemption from the new drug approval requirements for compounded drugs that comply with conditions explicitly delineated in FDAMA.

A.

[6] [7] At the first step of a *Chevron* analysis, we must determine whether "Congress has directly spoken" in a manner that reveals its "expressed intent." *Chevron*, 467 U.S. at 842–43, 104 S.Ct. 2778. There is no better or more authoritative expression of congressional intent than the statutory text: "[I]n all statutory construction cases, we begin with the language of the statute." *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 450, 122 S.Ct. 941, 151 L.Ed.2d 908 (2002). And where "the statutory language is unambiguous and the statutory scheme is coherent and consistent," the language of the statute is usually where we end.[22]

[8] The FDCA defines "new drug" in § 321(p) as follows:

> The term "new drug" means
>
> > (1) *Any drug* (except a new animal drug or an animal feed bearing or containing a new animal drug) the *composition of which* is such that such drug is *not generally recognized*, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, *as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.* ...

§ 321(p)(1) (emphasis added). The latter portion of this definition—"not generally recognized ... as safe and effective"—invokes the statutory standard a drug must meet to gain FDA approval. *See* § 355(d). Hence, "any drug ... the composition of which" has not already been approved by the FDA constitutes a "new drug" within the meaning of the statute. And the FDCA makes it unlawful to dispense a "new drug" without establishing the safeness and effectiveness of the new drug through the FDA approval process:

> No person shall introduce or deliver for introduction into interstate commerce any *new drug*, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

§ 355(a) (emphasis added). In other words, if a drug has not already been approved, it is a "new drug" that must first be approved before it can be dispensed. The term "drug" is also given a broad definition, which includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." § 321(g)(1)(B).

***395** The FDA argues that the language of the FDCA's "new drug" definition is both plain and expansive. A "new drug" is "*any* drug" the "composition of which" has not already been approved for use in accordance with its labeling. Compounded drugs are, after all, drugs. If a compounder changes the composition of an approved drug—by mixing or combining an approved drug with something else to create a different substance or by creating special dosage or delivery forms of an approved drug inconsistent with a drug's labeling[23]—the composition of the individualized concoction created by a compounding pharmacist will not have been previously approved for use. The resulting substance is therefore a "new drug."

[9] Belying the Pharmacies' argument that compounded drugs are not "new drugs" by virtue of their creation by licensed pharmacists, the definition of "new drug" focuses on the drug's composition and use rather than on the process by which it was created. Under the plain language of § 321(p)(1), it does not matter that the substance has been created through compounding rather than manufacturing—whether it be through rigorous research and development by a pharmaceutical company, through individualized compounding by a pharmacist or through cut-rate production by a rogue manufacturer. Regardless of how and by whom it was created, "any" such substance constitutes a "new drug" within the meaning of § 321(p)(1).

[10] Moreover, the FDCA carves out specific exceptions to the sweeping "new drug" definition for some "grandfathered" old drugs, *see* § 321(p)(1), and for drugs intended only for investigational use, *see*

Congress creates specific exceptions to a broadly applicable provision, the "proper inference ... is that Congress considered the issue of exceptions and, in the end, limited the statute to the ones set forth." *United States v. Johnson*, 529 U.S. 53, 58, 120 S.Ct. 1114, 146 L.Ed.2d 39 (2000). The "new drug" definition contains no general exception for drugs created by compounding.

The district court found no significant textual argument for exempting compounded drugs and, instead, shuffled briskly past the statute's text in search of its purpose.[24] The Pharmacies do little more in their briefs on appeal, except to argue that "[t]he word 'any' does not always mean 'all.' "[25] The Pharmacies cite Webster's Dictionary for the proposition that "any" can mean "one, a, an, or some." ***396** They do not explain the implications of that assertion, however, and for good reason: Substituting those words for "any" in the text of § 321(p) would hardly change its meaning. The Pharmacies seek instead to swap the words "any drug" for something like "only those drugs not compounded by a pharmacy." But neither the word "any" nor its textual context permits such linguistic creativity.

B.

[11] [12] Although the plain language of § 321(p) does not seem ambiguous as applied to compounding, the district court and the Pharmacies rely on their view of the FDCA's purpose as a trump against the statute's text. Upon discovering that a statute's plain text is in tension with its supposed purpose, one usually concludes that Congress has spoken ambiguously. Yet, for us to reject the FDA's interpretation of § 321(p), *Chevron* requires the Pharmacies to establish more than ambiguity; it demands that we defer to the agency's statutory interpretation unless it is contrary to Congress's "*unambiguously* expressed intent." 467 U.S. at 843, 104 S.Ct. 2778 (emphasis added). Pharmacies can therefore avoid *Chevron* deference only by establishing that congressional intent is in fact not ambiguous—that the statute's purpose is so clear and compelling, despite tension with its plain text, that it leaves no doubt as to Congress's intent. That is a heavy burden.

[13] The burden is somewhat eased, however, by what has come to be known as the "elephant-in-mousehole doctrine" first invoked in *Whitman v. American Trucking Associations*, 531 U.S. 457, 468, 121 S.Ct. 903, 149 L.Ed.2d 1 (2001):

> [R]espondents must show a textual commitment of authority to the EPA to consider costs.... Congress, we have held, does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes.

American Trucking's elephant-in-mousehole doctrine reaffirmed similar reasoning in *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 120 S.Ct. 1291, 146 L.Ed.2d 121 (2000). There, the Court held that nicotine was not a "drug" within the meaning of the FDCA and thus could not be regulated by the FDA. Although nicotine seemed to fit the FDCA's technical definition of a "drug," the Court declared, "we are confident that Congress could not have intended to delegate a decision of such economic and political significance to an agency in so cryptic a fashion." *Brown & Williamson*, 529 U.S. at 160, 120 S.Ct. 1291.

Most recently, the Court applied the elephant-in-mousehole doctrine in *Gonzales v. Oregon*, 546 U.S. 243, 126 S.Ct. 904, 163 L.Ed.2d 748 (2006), holding that the Attorney General lacks authority under the physician-registration provision of the Controlled Substances Act ("CSA") to prohibit doctors from prescribing drugs for use in physician-assisted suicide. Citing *American Trucking* and *Brown & Williamson*, the Court found implausible "[t]he idea that Congress gave the Attorney General such broad and unusual authority through an implicit delegation in the CSA's registration provision." *Gonzales*, 546 U.S. at 267, 126 S.Ct. 904.[26]

***397** The Pharmacies argue, in essence, that this is an elephant-in-mousehole case. They suggest that including compounded drugs under the FDCA's "new drug" definition would effectively outlaw the common practice of compounding and that the "new drug" definition is too broad and indefinite to indicate congressional intent for such result. In other words, Congress hid no such elephant in § 321(p)'s mousehole.

The Pharmacies reason that Congress never intended to regulate traditional pharmacy compounding and that the FDCA's "new drug" provision was intended only to cover drugs produced through large-scale manufacturing. The Pharmacies contend that at the time of the FDCA's enactment, compounding was adequately regulated by the states, and the FDCA was passed in response to a perceived lack of oversight of drug manufacturing, not compounding. To apply the provision to compounded drugs, the Pharmacies argue, would cause an extraordinary expansion of the FDA's regulatory

authority.

To support their view of congressional intent, the Pharmacies quote two statements from the FDCA's legislative history. The President of the American Pharmaceutical Association told a subcommittee of the Senate Committee on Commerce the following:

> Regulations governing ... the practice of pharmacy by pharmacists are very strict, but the privileges of unlicensed persons operating outside of pharmacies are so extensive that the public enjoys little protection in the matter of sales of packaged medicines.[27]

In a similar vein, Representative Coffee made remarks to the House, approvingly quoting the Secretary of Agriculture:

> Pharmacists are licensed to compound and dispense drugs. Electricians, plumbers, and steam engineers pursue their respective trades under license. But there is no such control to prevent incompetent drug manufacturers from marketing any kind of lethal poison.[28]

[14] "Floor statements from two Senators cannot amend the clear and unambiguous language of a statute." *Barnhart*, 534 U.S. at 457, 122 S.Ct. 941. The Court has seen "no reason to give greater weight to the views of two Senators than to the collective votes of both Houses, which are memorialized in the unambiguous statutory text." *Id.* The same, or less, might be said for subcommittee testimony by an industry spokesman and a statement by a Representative.

These bits of legislative history, moreover, establish only that their speakers were concerned about regulating drug manufacturing; they do not express any plain intent to refrain from further regulating the drugs created through pharmacy compounding. To the contrary, "statutory prohibitions often go beyond the principal evil to cover reasonably comparable evils, and it is ultimately the provisions of our ***398** laws rather than the principal concerns of our legislators by which we are governed." *Oncale v. Sundowner Offshore Servs., Inc.*, 523 U.S. 75, 79, 118 S.Ct. 998, 140 L.Ed.2d 201 (1998).[29]

Given the apparent ubiquity of pharmacy compounding at the time Congress passed the FDCA, it would have been unprecedented for the FDCA to regulate compounded drugs. But the same can be said for drugs produced through manufacturing, which had also not previously been regulated by the federal government. The mere prevalence of a practice hardly establishes the obvious intent not to regulate it.[30] Nevertheless, it seems unlikely that Congress intended to force compounded drugs to undergo the new drug approval process, a requirement that would have made compounding nearly impossible and thus nonexistent.[31] Construing the "new drug" definition in a way that makes compounding effectively unlawful appears inconsistent with the likely expectation that compounding would and should persist[32] and with other provisions of the FDCA that expressly acknowledge the existence of compounding.[33]

But this does not quite amount to the *reductio ad absurdum* it might at first seem to be. There are two reasons, one small and one large, why the universally-appreciated practice of compounding would not be extinguished by including compounded drugs within the "new drug" definition. First, if one considers "compounding" to include creating specialized dosage forms consistent with the instructions on a drug's label, that would be a kind of compounding that would not result in a "new ***399** drug" under the FDCA's definition.[34] That sort of on-label compounding would be perfectly permissible even without exempting compounded drugs from the "new drug" definition.

Second, and more significantly, even if compounded drugs are effectively made unlawful by the "new drug" definition and approval requirements, pharmacists still could continue compounding to the extent allowed by the FDA's enforcement discretion. The FDA did not enforce the "new drug" requirement against traditional compounding for decades, and the agency's Compliance Policy Guide declared only a limited intention to conduct future enforcement in cases in which compounding looks more like disguised manufacturing. The FDCA explicitly permits the FDA to decline enforcement of "minor violations." 21 U.S.C. § 336, and this court has affirmed such discretion in an analogous context, observing, "Although the [FDCA] makes illegal any amount of substance which 'may render (food) injurious to health' the FDA is not required to seek to enjoin, prosecute or otherwise litigate 'minor violations' of the Act," *United States v. Boston Farm Ctr., Inc.*, 590 F.2d 149, 151 (5th Cir.1979) (citations omitted).

Indeed, the Supreme Court has suggested that we should not infer an absurd result from a maximalist interpretation of the FDA's authority where such authority is tempered by enforcement discretion.[35] When it comes to the slippery task of distinguishing true compounding from disguised manufacturing, we should question our own

capacity, as a court, to make that distinction in future cases. In exercising its discretion, the FDA relies on numerous factors and considerations to determine whether a pharmacist is engaged in compounding as distinguished from manufacturing.[36] With no guidance from the statutory text, we doubt we could do any better, and we are wary of trading the FDA's discretion for our own.

The Pharmacies may quite understandably find cold comfort in the FDA's promised self-restraint. In light, however, of the agency's statutorily-authorized enforcement discretion and demonstrated willingness to accommodate traditional compounding's continued existence, there is reason to think pharmacies would continue to compound even if compounded drugs were deemed "new drugs." Construing the FDCA to give the FDA authority over compounding would thus not necessarily "lead to a result so bizarre that Congress could not have intended it." *Johnson,* 120 F.3d at 1319 (quotation omitted).

Nonetheless, it remains at least questionable that Congress would have intended ***400** such a large expansion of the FDA's regulatory authority. And it remains no small burden for compounding pharmacists, as they put it, to "live in sin"—their livelihood having no greater assurance than the FDA's good graces.

C.

With only the original FDCA's text, the elephant-in-mousehole doctrine, and the uncertain evidence of congressional intent, this might have been a difficult case. A subsequent amendment to the FDCA, however, makes it easy.

In 1997, Congress enacted FDAMA as an amendment to the FDCA. That amendment provides considerable evidence that Congress sought to address pharmacy compounding directly and that it did so with the assumption that the "new drug" provision applies to drugs created through pharmacy compounding. Moreover, FDAMA alters the FDCA in such a way that reading an implicit compounding exemption into the "new drug" definition would render other crucial parts of the statute superfluous. If we read the FDCA in light of its amendment in FDAMA, Congress's intent to include compounded drugs within the FDCA's "new drug" definition becomes obvious: That intent becomes a necessary component of the amended statutory scheme; and the feared chilling effect on the common practice of compounding becomes a much diminished concern. Whatever might have been Congress's intent regarding compounding when it drafted the FDCA, FDAMA substantially clarifies it.

There is potential trouble in relying on FDAMA, however, because the validity of that amendment remains uncertain. In *Western States,* the Supreme Court struck down the advertising provision of FDAMA but left open the question whether the remaining portions of the statute were non-severable and thus invalid in light of the stricken provision.[37] Both sides here argue that we need not decide the severability question, because we may look to FDAMA as evidence of Congress's understanding of the FDCA's "new drug" provision, regardless of whether FDAMA survives *Western States.* We disagree and therefore find it necessary to address severability.

[15] [16] "Over time, ... subsequent acts can shape or focus" a statute's "range of plausible meanings," and "[t]his is particularly so where the scope of the earlier statute is broad but the subsequent statutes more specifically address the topic at hand." *Brown & Williamson,* 529 U.S. at 143, 120 S.Ct. 1291. It is the act of subsequent amendment that most significantly alters the meaning of a statute by altering the statutory scheme as a whole and thereby affecting the context of a prior Congress's enactment.[38] Where a subsequent Congress has *not* enacted a valid amendment, however, the intent of the prior Congress is the best guide to the meaning of the statute it promulgated. We must heed the "oft-repeated warning that 'the views ***401** of a subsequent Congress form a hazardous basis for inferring the intent of an earlier one.' "[39] Hence, absent a valid amendment to alter the statutory structure, the opinion of the 1997 Congress informs us little in deciding what the 1937 Congress intended when it drafted the "new drug" definition.

[17] In short, Congress's act of amendment gains lawful expression only through enactment of a valid statute.[40] If that act of amendment is invalid—for instance, because its unconstitutional portions cannot be severed—the act is *void ab initio,* and it is as though Congress had not acted at all. Accordingly, to rely on FDAMA in construing the "new drug" definition, we first must address FDAMA's validity. After doing so, we consider precisely how FDAMA affects interpretation of the "new drug" definition.

1.

[18] In the supplemental briefing, the FDA argues against severability, and the Pharmacies argue in favor of it. The

Ninth Circuit held that FDAMA is not severable. *See Shalala,* 238 F.3d at 1096–98. Agreeing with the Pharmacies and differing with the FDA and the Ninth Circuit, we conclude that the invalidated portion of FDAMA is severable and that its surviving portions therefore remain in effect.

[19] [20] The Supreme Court has summed up the "well established" standard for severability: "Unless it is evident that the Legislature would not have enacted those provisions which are within its power, independently of that which is not, the invalid part may be dropped if what is left is fully operative as a law." *Alaska Airlines, Inc. v. Brock,* 480 U.S. 678, 684, 107 S.Ct. 1476, 94 L.Ed.2d 661 (1987) (internal quotation omitted). This standard hinges decisively on congressional intent such that the "relevant inquiry in evaluating severability is whether the statute will function in a *manner* consistent with the intent of Congress." *Id.* at 685, 107 S.Ct. 1476 (emphasis added).

[21] One crucial clue to that intent is Congress's decision to include an express severability provision in the statute. FDAMA amended Section 353 of Title 21 of the United States Code, which codifies the FDCA.[41] Although FDAMA contains ***402** no severability clause, Section 391 provides as follows:

> If any provision of this chapter is declared unconstitutional, or the applicability thereof to any person or circumstances is held invalid, the constitutionality of the remainder of the chapter and the applicability thereof to other persons and circumstances shall not be affected thereby.
> 21 U.S.C. § 391.

[22] In *Koog v. United States,* 79 F.3d 452 (5th Cir.1996), we faced a similar situation involving the severability of parts of an amendment to a statute. The statute had a severability clause substantially the same as the clause here, but the amendment had no such clause. We held that where its express intent was to amend a statute, "[w]e can only assume that Congress was fully aware of [the statute's severability clause] when it chose to insert the [amendment] into Title 18, and that Congress intended the severability provision to apply equally to the [amending] provisions." *Id.* at 463. The same assumption is warranted here, so "a presumption of severability arises" that "may be overcome only by 'strong evidence' that Congress would not have enacted the law without the invalidated portions of the statute." *Id.* at 462 (quoting *Alaska Airlines,* 480 U.S. at 686, 107 S.Ct. 1476).[42]

FDAMA carves out an exception to the new drug approval process for compounding pharmacists who comply with a number of specific, mandatory requirements. One of those requirements, which permitted pharmacists to advertise compounding *services* but barred them from advertising specific compounded *drugs,* was the portion of FDAMA the Court invalidated in *Western States.* FDAMA contained numerous other requirements, however, which the Court enumerated and summarized as follows:

> First, [the compounded drugs] must be compounded by a licensed pharmacist or physician in response to a valid prescription for an identified individual patient, or, if prepared before the receipt of such a prescription, they must be made only in "limited quantities" and in response to a history of the licensed pharmacist's or physician's receipt of valid prescription orders for that drug product within an established relationship between the pharmacist, the patient, and the prescriber. 21 U.S.C. § 353a(a).
>
> Second, the compounded drug must be made from approved ingredients that meet certain manufacturing and safety standards, §§ 353a(b)(1)(A)-(B), and the compounded drug may not appear on an FDA list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or ineffective, § 353a(b)(1)(C).
>
> Third, the pharmacist or physician compounding the drug may not "compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product." § 353a(b)(1)(D).
>
> ***403** Fourth, the drug product must not be identified by the FDA as a drug product that presents demonstrable difficulties for compounding in terms of safety or effectiveness. § 353a(b)(3)(A).
>
> Fifth, in States that have not entered into a "memorandum of understanding" with the FDA addressing the distribution of "inordinate amounts" of compounded drugs in interstate commerce, the pharmacy, pharmacist, or physician compounding the drug may not distribute compounded drugs out of state in quantities exceeding five percent of that entity's total prescription orders. § 353a(b)(3)(B).
>
> Finally, and most relevant for this litigation, the prescription must be "unsolicited," § 353a(a), and the pharmacy, licensed pharmacist, or licensed physician compounding the drug may "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," § 353a(c). The pharmacy, licensed pharmacist, or licensed physician may, however, "advertise and promote the compounding service."

Ibid.

W. States, 535 U.S. at 364–65, 122 S.Ct. 1497 (paragraph breaks added).

The Ninth Circuit reasoned that FDAMA was "intended to provide access to compounded drugs while preventing pharmacies from making an end run around the FDA's drug manufacturing requirements." *W. States*, 238 F.3d at 1096. Congress wanted to permit access to compounded drugs on a small scale while preventing compounding pharmacies from acting like large-scale manufacturers, which would subvert the FDCA's new drug approval and other requirements. To that end, FDAMA's advertising restrictions help limit demand for large-scale compounding. Thus, according to the Ninth Circuit, the unconstitutional advertising portions of FDAMA were such a key part of Congress's careful balance that "Congress would not have passed FDAMA absent the restrictions on commercial speech." *Id.* at 1097.

Although we generally agree with the Ninth Circuit's understanding of FDAMA's purpose and the advertising provision's role in furthering it, we do not see the advertising provision as so central to the purpose of FDAMA that Congress would not have passed the statute without it. The advertising requirement indeed helped further Congress's intended balance, but so did FDAMA's five other requirements mentioned above. Much like the advertising provision, those other requirements function to create permissible space for compounding pharmacists while limiting pharmacists' ability to engage in large-scale manufacturing.

[23] Severing the advertising requirement would leave those other considerable requirements intact, and they would continue to effect Congress's purpose.[43] ***404** Where a statute's invalidated provision is one of a series of conditions, each of which is designed to promote a common goal, courts have deemed such a statute severable.[44] In light of the five other requirements in FDAMA, excising the advertising provision would not render FDAMA "incapable of functioning independently." *Alaska Airlines*, 480 U.S. at 684, 107 S.Ct. 1476.

The Ninth Circuit also relied on legislative history to divine Congress's intent, which is inconclusive at best. The Ninth Circuit argued that Congress added the advertising-related provision to FDAMA after the FDA Commissioner had pointed out that the proposed version of the bill " 'has no constraints on the volume of compounding,' " " 'would allow bulk drug suppliers or drug manufacturers to circumvent the approval requirements,' " and " 'is likely to develop ... a shadow industry of unapproved generic drugs.' " *W. States*, 238 F.3d at 1097 (quoting FDA Commissioner's statement to House subcommittee).

The Ninth Circuit concluded that the subsequent decision to add the advertising provision, which reduced the threat of high-volume compounding, suggests that Congress would not have passed FDAMA without the advertising provision. *Id.* That conclusion does not follow. The mere fact (or rather, assumption) that Congress responded to the FDA's concerns does not mean that it would have refrained from enacting the bill if it could not have satisfied those concerns. The Ninth Circuit's suppressed premise—and as far as we are aware, a premise unsupported by the legislative history—is that satisfying the FDA was necessary to passage of the legislation.

Moreover, and perhaps more significantly, the advertising provision was merely one of multiple provisions added to the original bill in response to the FDA's concerns. The restrictions on compounding copies of commercially available drugs, the safety restrictions, and the restrictions on out-of-state distribution were added in subsequent versions of the bill, and all respond to the FDA's same basic concern of limiting the volume of unregulated manufacturing disguised as compounding.[45] Therefore, even assuming it would not have enacted the bill without allaying FDA's concerns, Congress had multiple ways of doing so. The advertising provision was one way, and the other three provisions added to the original bill were alternate ways. It is unfounded, on the basis of this legislative history alone, to elevate the advertising provision over the others and treat it as a necessary provision without which the bill would not have passed.

Neither FDAMA's text nor the inconclusive legislative history amounts to " 'strong evidence' that Congress would not have enacted the law without" the advertising provisions. *Koog*, 79 F.3d at 462 (quoting ***405** *Alaska Airlines*, 480 U.S. at 686, 107 S.Ct. 1476). Far from strong, the evidence is at best inconclusive. We therefore apply the statute's explicit severability provision, and FDAMA is severable.

2.

Because FDAMA remains valid, we must construe the FDCA's "new drug" definition in light of it. FDAMA distinguishes between compounding and manufacturing in much the same way as the Pharmacies urge us to narrow the "new drug" definition. It does so, however, not by changing the definition of "new drug" but instead by

explicitly "exempt[ing] compounded drugs from the FDCA's 'new drug' requirements and from other requirements provided the drugs satisfy a number of restrictions." *W. States*, 535 U.S. at 364, 122 S.Ct. 1497. Accordingly, compounded drugs are not exempt from the FDCA's "new drug" *definition*, § 321(p), nor are they uniformly exempt from the FDCA's "new drug" *requirements*, §§ 351(a)(2)(B), 352(f)(1), 355. Rather, compounded drugs are in fact "new drugs" as defined by § 321(p) but are exempt from the requirements of §§ 351(a)(2)(B), 352(f)(1), and 355 if and only if they comply with the conditions set forth in § 353a.

FDAMA's conditional exemption reads in part as follows:

> Sec. 353a. Pharmacy compounding
>
> (a) In general
>
> > Sections 351(a)(2)(B) [adulteration provision], 352(f)(1) [misbranding provision], and 355 [new drug approval provision][46] of this title *shall not apply* to a drug product *if the drug product is compounded* for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, *if the drug product meets the requirements of this section*, and if the compounding [is done by a licensed pharmacist or physician].

§ 353a(a) (emphasis added). FDAMA thus creates a safe harbor for compounding but does so in a particularly significant way within the context of the statute. It does not outlaw all compounding or create a general limitation on the FDA's authority over traditional compounding. Instead, it starts from the default premise that the FDCA's adulteration, misbranding, and new drug approval provisions apply to—and thereby restrict—all drugs created by any means.

Against that statutory background, FDAMA instructs that the adulteration, misbranding, and "new drug" approval provisions "shall not apply ... *if* the drug product is compounded" and "*if* the drug product meets the requirements" of FDAMA. The requirements themselves are thus not freestanding but instead serve to trigger an exemption from the adulteration, misbranding, and new drug approval provisions. If the requirements are not met, the exemption does not apply.

The district court and the Pharmacies reach a different construction of the statute whereby § 321(p)'s definition of "new drug" contains a categorical "implicit" exemption for compounded drugs wholly apart from the narrow, conditional, and ***406** explicit exceptions enumerated in § 353a. We disagree, because reading the "new drug" definition implicitly to exclude compounded drugs would make § 353a's explicit, conditional exceptions superfluous.

[24] It is "a cardinal principle of statutory construction" that a statute be construed such that "no clause, sentence, or word shall be superfluous, void, or insignificant." *Duncan v. Walker*, 533 U.S. 167, 174, 121 S.Ct. 2120, 150 L.Ed.2d 251 (2001) (quotation omitted). If, by the Pharmacies' desired construction, compounded drugs are not "new drugs," it would make no sense for § 353a to state that the "new drug" approval provision "does not apply ... if the [compounded] drug product meets the requirements of this section." Under the Pharmacies' construction, the compounded drug would be immune from the new drug approval provision regardless of whether it "met the requirements" of § 353a. The Pharmacies' construction of the "new drug" definition would thereby render much of § 353a superfluous.

The Pharmacies counter by claiming that Congress enacted FDAMA to "clarify" that it "never intended" to include compounded drugs within the "new drug" definition. The Pharmacies contend that "[n]owhere in the legislative history of FDAMA does Congress state ... that it intended for FDAMA to serve as a new statutory exemption for pharmacies from the 'new drug' requirements." Though Congress might not have stated in the legislative history its intention to create such an exemption, it did say that plainly in the statute itself—"shall not apply ... if"—and we need not entertain negative implications from the legislative history in the face of plain statutory text.

The Pharmacies also argue that "Congress enacted FDAMA to prevent FDA from regulating pharmacy compounds as 'new drugs' in the face of FDA's attempt to do so." As support, they quote a Senate committee report that notes, "The committee has found that clarification is necessary to address current concerns and uncertainty about [the FDA's] regulatory authority over pharmacy compounding."[47] That snippet of legislative history, however, tells us nothing about *how* Congress intended to "clarify" uncertainty over the FDA's authority; for that, we must look to the statute itself. Congress easily could have "clarified" the uncertainty by amending and limiting the "new drug" definition directly; instead, in promulgating § 353a, it created a conditional exception triggered by numerous very specific new statutory requirements. The conditional exception makes sense only if the "new drug" definition is construed to

apply to compounded drugs.

[25] In summary, 321(p)'s definition of "new drug" applies to drugs created by compounding. Because compounded drugs are "new drugs," the restrictions on "new drugs" set forth in §§ 351(a)(2)(B), 352(f)(1), and 355 generally apply to compounded drugs. Against that backdrop, however, § 353a carves out explicit, conditional exceptions for compounded drugs that comply with its enumerated conditions. If and only if the compounded drugs satisfy § 353a's conditions, those drugs are exempt from the requirements of §§ 351(a)(2)(B), 352(f)(1), and 355.

IV.

[26] The district court also considered application of the FDCA to compounded drugs designed for animal use. If it has ***407** not been approved, a "new animal drug" is "adulterated" under § 351(a)(5) and "unsafe" under § 360b(a)(1).[48] An unapproved "new animal drug" created from bulk ingredients and lacking "adequate directions for use" is "misbranded" under § 352(f) and FDA regulations.[49] Hence, to avoid being deemed "adulterated," "unsafe," or "misbranded," a drug product compounded by a veterinarian must either go through the new animal drug approval process or fall outside the definition of "new animal drug."

The district court concluded, and the Pharmacies argue, that drug products compounded in bulk by pharmacists and veterinarians are not "new animal drugs" and therefore are not "adulterated," "unsafe," or "misbranded" (when lacking "adequate directions for use"). We conclude, to the contrary, that compounded drugs are "new animal drugs" under the FDCA.

[27] The FDCA defines "new animal drug" in a manner substantially identical to its definition of "new [human] drugs":

> (v) The term "new animal drug" means *any drug* intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed,—
>
> > (1) *the composition of which* is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof....

§ 321(v)(1). Hence, similarly to human drugs, "any drug ... the composition of which" has not already been approved by the FDA constitutes a "new animal drug" within the meaning of the statute.

Although FDAMA's conditional exception to the FDCA's new drug definition applies only to human drugs, Congress passed a similar amendment to the FDCA relating to animal drugs, AMDUCA, that exempted compounded "new animal drugs" from the new drug approval process in certain circumstances:

> (4)(A) Except as provided in subparagraph (B) [FDA finding that use of the drug would present health risk], *if an approval* of an application filed under subsection (b) [new animal drug approval provision] is in effect with respect to a *particular use or intended use of a new animal drug*, the drug *shall not be deemed unsafe* for the purposes of paragraph (1) and shall be exempt from the requirements of section 352(f) of this title *with respect to a different use or intended use of the drug*, other than a use in or on animal feed, *if* such use or intended use—
>
> > (i) is by or on the *lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship*, as defined by the Secretary; and
> >
> > ***408** (ii) is in compliance with regulations promulgated by the Secretary that establish the conditions for such different use or intended use....
>
> (5) *If the approval* of an application filed under section 355 of this title [new human drug approval provision] is in effect, the drug under such application *shall not be deemed unsafe* for purposes of paragraph (1) and shall be exempt from the requirements of section 352(f) of this title *with respect to a use or intended use of the drug* in animals *if* such use or intended use—
>
> > (A) *is by or on the lawful written or oral order of a licensed veterinarian within the context of a veterinarian-client-patient relationship*, as defined by the Secretary; and
> >
> > (B) is in compliance with regulations promulgated by the Secretary that establish the conditions for the use or intended use of the drug in animals.

§ 360b(a)(4), (5) (emphasis added).

Accordingly, paragraph (4) establishes that if a new animal drug is approved for one animal use, it can be used for a different unapproved use (*i.e.*, compounded), and

paragraph (5) provides that if a new drug is approved for human use, it can be used for a different unapproved animal use (*i.e.*, compounded). In both cases, the drug must be used pursuant to the order of a licensed veterinarian and is subject to the FDA's discretionary finding that it poses a risk to public health.

Although its provisions are different from FDAMA's, AMDUCA's effect on construction of the "new animal drug" definition is much the same as FDAMA's effect on construction of the "new [human] drug" definition. AMDUCA suggests that the FDCA's use of the term "new animal drug" includes compounded drugs. If the definition of "new animal drug" excluded compounded drugs, and thereby did not trigger the new drug approval process for compounded drugs, the compounded drugs would not be deemed "unsafe" within the meaning of § 360b(a)(1) and would not be deemed "misbranded" within the meaning of § 352(f). But if that were so, it would render superfluous AMDUCA's requirement that certain compounded drugs "shall not be deemed unsafe ... and shall be exempt from the requirements of [§ 352(f)] ... *if*" they comply with AMDUCA's conditions.

We therefore conclude, in agreement with the two other circuits that have considered the issue,[50] that compounded drugs are "new animal drugs" within the meaning of § 321(v)(1) of the FDCA. And unless the compounded drugs are exempt under the FDCA's AMDUCA provisions, § 360b(a)(4) and (5), compounded animal drugs are subject to the FDCA's unsafe, adulteration, and misbranding requirements. As with human drugs, the FDCA contains no blanket "implicit exemption" for animal drugs produced by compounding.

V.

In summary, compounded drugs are not subject to a general exemption from the definitions of "new drug" and "new animal drug" contained in § 321(p)(1) and (v)(1). ***409** But because the severed portions of FDAMA are valid and in force, new human drugs that result from compounding are exempt from the adulteration, misbranding, and new drug approval provisions of §§ 351(a)(2)(B), 352(f)(1), and 355 if they comply with the conditions in § 353a. Likewise, new animal drugs that result from compounding are exempt from the unsafe, adulteration, and misbranding provisions of §§ 360b(a)(1), 351(a)(5), and 352(f) if they comply with the conditions in § 360b(a).

The judgment is VACATED and REMANDED for further proceedings as appropriate in accordance with this opinion.

All Citations

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Footnotes

1 *See Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360–61, 122 S.Ct. 1497, 152 L.Ed.2d 563 (2002) (defining compounding); *Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 (5th Cir.1995) (same).

2 *See* CHARLES H. LAWALL, THE CURIOUS LORE OF DRUGS AND MEDICINES (FOUR THOUSAND YEARS OF PHARMACY) 485 (1927).

3 21 U.S.C. § 351(b) (referencing the *U.S. Pharmacopeia*'s strength, quality, and purity standards).

4 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application [by the FDA] is effective with respect to such drug.").

5 21 U.S.C. § 321(p)(1).

6 *See* 21 U.S.C. § 360b(a)(1) ("A new animal drug shall, with respect to any particular use or intended use of such drug, be deemed unsafe ... unless ... there is in effect an approval of an application filed [with the FDA].").

7 *See* 21 U.S.C. § 321(v)(1) (defining "new animal drug" as "any drug intended for use for animals other than man ... the composition of which is such that such drug is not generally recognized ... as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof").

8 *See* 21 U.S.C. § 355(b) (detailing process for new human drugs), § 360b(b) (detailing process for new animal drugs).

9 *See* 21 U.S.C. § 355(d), (e); *Weinberger v. Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609, 630, 93 S.Ct. 2469, 37 L.Ed.2d 207 (1973) ("The Act requires the Commissioner to disapprove any application when there is a lack of 'substantial evidence' that the applicant's drug is effective.").

10 *Weinberger,* 412 U.S. at 630, 93 S.Ct. 2469. "Evidence may be accepted only if it consists of 'adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved....' The 'substantial evidence' requirement reflects the conclusion of Congress, based upon hearings, that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy." *Id.* (citations omitted).

11 *See, e.g.,* Joseph A. DiMasi, *et al., The Price of Innovation: New Estimates of Drug Development Costs,* 22 J. HEALTH ECON. 151 (2003).

12 In considering whether the FDA could deem bulk animal drugs held by a middleman and intended for veterinarian compounding to be unlawfully "misbranded" under the FDCA, the Seventh Circuit has observed the following:

> No one may sell a new animal drug, or feed containing a new animal drug, without the approval of the Food and Drug Administration. Obtaining approval takes a long time and costs a lot of money, for the FDA requires thorough experimentation to determine both the drug's effects on animals and whether its residues persist in the animals and enter the food chain.... We must take it as given that for significant diseases there are no effective FDA-approved drugs.... Many veterinarians find this state of affairs deplorable. Because they cannot buy in finished form the drugs they think they should be able to use, they have elected to make their own. They purchase the active ingredients, mix them in the proportions they think best, and administer their concoctions as professional judgment dictates.

United States v. 9/1 Kg. Containers, 854 F.2d 173, 174–75 (7th Cir.1988) (citations omitted); *see also United States v. Algon Chem., Inc.,* 879 F.2d 1154, 1155–56 (3d Cir.1989) ("No veterinarian currently holds a [new animal drug application]; [the applications] are apparently held exclusively by pharmaceutical and animal feed companies which, unlike the veterinarians, have the resources to develop and test the drugs according to the rigors of the Act.").

13 *See W. States,* 535 U.S. at 362, 122 S.Ct. 1497; *Prof'ls & Patients,* 56 F.3d at 593 n. 3.

14 *See W. States,* 535 U.S. at 362, 122 S.Ct. 1497 (summarizing rationale); *Professionals & Patients,* 56 F.3d at 593 (same).

15 The agency would consider whether the pharmacy engaged in any of the following practices:

> 1. Soliciting business ... to compound specific drug products....
> 2. Compounding, regularly, or in inordinate amounts, drug products that are commercially available in the marketplace and that are essentially generic copies of commercially available, FDA-approved drug products.
> 3. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-approved facility.
> 4. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
> 5. Using commercial scale manufacturing or testing equipment or compounding drug products.
> 6. Compounding inordinate amounts of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions.
> 7. Offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
> 8. Distributing inordinate amounts of compounded products out of state.
> 9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

CPG 7132.16, at 5.

16 *W. States,* 535 U.S. at 364, 122 S.Ct. 1497 ("Congress turned portions of [the FDA's 1992] policy into law when it enacted FDAMA in 1997. FDAMA, which amends the FDCA, exempts compounded drugs from the FDCA's 'new drug' requirements and other requirements provided the drugs satisfy a number of restrictions.").

17 *See* FDA Compliance Policy Guide Sec. 460.200, Pharmacy Compounding (May 2002) ("CPG 460.200") (human drugs); FDA Compliance Policy Guide Sec. 608.400, Compounding of Drugs for Use in Animals (July 2003) ("CPG 608.400") (animal drugs).

18 For human drugs, these factors are very similar to the factors listed in the 1992 Guide, *supra* note 15, except that the FDA dropped the earlier Guide's factors relating to advertising and out-of-state distribution and added two new factors:

> 2. Compounding drugs that were withdrawn or removed from the market for safety reasons....
> 3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application....

CPG 460.200, at 3–4. The thirteen factors applying to animal drugs are similar, though not identical. CPG 608.400, at 4–5.

19 The full list of requested declarations and injunctions totaled thirteen. *See Med. Ctr. Pharmacy v. Gonzales,* 451 F.Supp.2d 854, 856 (W.D.Tex.2006).

20 The court also framed the Pharmacies' requested declaratory judgment as "a declaration that drugs compounded by licensed pharmacists are not 'new drugs' or 'new animal drugs' *per se* under 21 U.S.C. §§ 321(p)(1) and (v)(1)." *Med. Ctr. Pharmacy,* 451 F.Supp.2d at 856. And the court concluded that summary judgment was "granted on [the Pharmacies'] claim that compounded drugs do not fall under the new drug definitions." *Id.* at 865.

21 Although the Pharmacies argue in their supplemental brief that the FDA waived any challenge to the severability holding, we cannot agree. The FDA and the Pharmacies argued principally that we need not reach the severability question, but presumably in anticipation that we might reach the question, the FDA in its opening brief registered its opposition to that holding. *See* Brief of Defendants–Appellants at 28–29 & 29 n. 5.

> A party does not waive an issue merely by suggesting that the court need not reach it to render its decision, though of course, parties do waive an issue if they fail adequately to brief it. *United States v. Martinez,* 263 F.3d 436, 438 (5th Cir.2001). Here, however, the FDA stated its position on severability in the body of its brief, made an argument (albeit an austere one) in defense of that position, and cited relevant authority. *Compare, e.g., United States v. Thames,* 214 F.3d 608, 611 n. 3 (5th Cir.2000) (waiver for failing to include arguments in body of brief) with *United States v. Beaumont,* 972 F.2d 553, 563 (5th Cir.1992) (waiver for failing to "make *any argument whatsoever* ") and *L&A Contracting Co. v. S. Concrete Servs.,* 17 F.3d 106, 113 (5th Cir.1994) (waiver for failing to cite relevant authority).

22 *Robinson v. Shell Oil Co.,* 519 U.S. 337, 340, 117 S.Ct. 843, 136 L.Ed.2d 808 (1997) (quotation omitted); *see also, e.g., Garcia v. Gloor,* 618 F.2d 264, 268 (5th Cir.1980) ("[W]e start with [the statute's] plain words without pausing to consider whether a statute differently framed would yield results more consonant with fairness and reason.").

23 *Amici* describe some specific practices that would be considered "compounding":

> Pediatric or geriatric patients may need extremely small doses, cancer patients may need specific combinations of chemotherapy drugs to treat their disease, or special dosage forms may be necessary to care for patients with AIDS, chronic pain or other maladies.... Still other patients need preservative-free products, liquids with special flavors, or delivery systems that are not commercially available.

Br. of Am. Pharmacists Ass'n as *Amici Curiae* for Appellees, at 8–9.

24 The district court stated, "Taken alone, the new drug definitions might seem to indicate that compound drugs fall within their provisions. However, after examining relevant case and statutory law, as well as legislative intent, this Court finds that compound drugs are implicitly exempt from the new drug definitions...." *Med. Ctr. Pharmacy,* 451 F.Supp.2d at 858.

25 Although " 'any' can and does mean different things depending upon the setting," *Nixon v. Mo. Mun. League,* 541 U.S. 125, 132, 124 S.Ct. 1555, 158 L.Ed.2d 291 (2004), the word generally "has an expansive meaning, that is, one or some indiscriminately of whatever kind," *Dep't of Housing & Urban Dev. v. Rucker,* 535 U.S. 125, 131, 122 S.Ct. 1230, 152 L.Ed.2d 258 (2002) (quotation omitted).

26 Other circuits have begun applying the elephant-in-mousehole doctrine. *Compare Am. Bar Ass'n v. F.T.C.,* 430 F.3d 457 (D.C.Cir.2005) (finding elephant-in-mousehole where Federal Trade Commission claimed authority under financial consumer privacy statute to regulate attorneys) *with Am. Fed'n of Gov't Employees, AFL–CIO v. Gates,* 486 F.3d 1316 (D.C.Cir.2007) (finding no elephant-in-mousehole where Department of Defense claimed authority under National Defense Authorization Act to curtail collective bargaining with civilian employees), *cert. dismissed,* 552 U.S. 1171, 128 S.Ct. 1183, 169 L.Ed.2d 959 (2008); *NISH v. Rumsfeld,* 348 F.3d 1263, 1269 (10th Cir.2003) (holding that "[w]e simply do not see the elephant in the mousehole" where the military claimed statutory authority to give blind vendors priority in awarding mess hall contracts).

27 *Foods, Drugs, and Cosmetics: Hearings Before a Subcomm. of the Comm. on Commerce,* 74th Cong. 100, 102 (1935) (statement of Robert P. Fischelis, President, American Pharmaceutical Ass'n) (quoting survey by committee on costs of medical care).

28 *Extension of Remarks of Rep. John M. Coffee,* 83 Cong. Rec. 2279, 2279 (June 1, 1938) (quoting Henry A. Wallace, Secretary of Agriculture).

29 *See also Brown & Williamson,* 529 U.S. at 147, 120 S.Ct. 1291 (deeming it "relevant" but "[o]f course ... not determinative" whether the Congress that enacted the FDCA specifically intended the Act to cover tobacco products).

30 *Cf. United States v. Sullivan,* 332 U.S. 689, 693, 68 S.Ct. 331, 92 L.Ed. 297 (1948) ("When it is reasonably plain that Congress meant its Act to prohibit certain conduct, [nothing] justifies a distortion of the congressional purpose, not even if the clearly correct purpose makes marked deviations from custom....").

31 By one estimate, pharmacists annually compounded more than 250 million prescriptions around the time of the FDCA's enactment, and the pharmacy laws of most states defined the practice of pharmacy to include compounding. *Proceedings of the Local Branches,* 24 J. AM. PHARM. ASS'NN 232, 233 (1935); *Joint Session of the American Pharmaceutical Association, the American Association of Colleges of Pharmacy and the National Association of Boards of Pharmacy,* 27 J. AM. PHARM. ASS'N 1000, 1010–13 (1938).

32 *Cf. Brown & Williamson,* 529 U.S. at 139, 120 S.Ct. 1291 ("Congress' decisions to regulate labeling and advertising ... reveal its intent that tobacco products remain on the market. Indeed, the collective premise of these statutes is that cigarettes and smokeless tobacco will continue to be sold in the United States. A ban of tobacco products by the FDA would therefore plainly contradict congressional policy.").

33 For example, provisions of the 1962 amendments to the FDCA exempt from registration and inspection requirements licensed "pharmacies ... which do not ... compound ... drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail." §§ 360(g)(1), 374(a)(2)(A). As the FDA points out, however, this reference to compounding cuts another way, as it also suggests Congress's awareness of compounding and its ability to create exceptions for compounding when it chooses to do so. That Congress chose not to do so with respect to the FDCA's "new drug" definition is instructive. Where " 'Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.' " *Russello v. United States,* 464 U.S. 16, 23, 104 S.Ct. 296, 78 L.Ed.2d 17 (1983) (quoting *United States v. Wong Kim Bo,* 472 F.2d 720, 722 (5th Cir.1972)).

34 The specialized dosage form would not be a new drug, because it would be a composition used "under the conditions prescribed, recommended, or suggested in the [approved] labeling" of the drug. § 321(p). *Amici* seem to admit this possibility: "The pharmaceutical manufacturers recognize the need for compounding, because they include instructions for compounding specialized dosage forms, such as oral suspensions, in some of their package inserts, which are the instructions for use that accompany any drug product and must be approved prior to distribution by the FDA." Br. of Am. Pharmacists Ass'n as *Amici Curiae* for Appellees, at 8 n. 6.

35 "The scope of the offense which Congress defined is not to be judicially narrowed as applied to drugs by envisioning extreme possible applications.... [The FDA] is given rather broad discretion—broad enough undoubtedly to enable [it] to perform [its] duties fairly without wasting [its] efforts on what may be no more than technical infractions of law." *United States v. Sullivan,* 332 U.S. at 694, 68 S.Ct. 331.

36 *See supra* notes 15, 18.

37 *See W. States,* 535 U.S. at 366, 122 S.Ct. 1497 ("We granted certiorari to consider whether FDAMA's prohibitions on soliciting prescriptions for, and advertising, compounded drugs violate the First Amendment. Because neither party petitioned for certiorari on the severability issue, we have no occasion to review that portion of the Court of Appeals' decision.") (citation omitted).

38 *See Brown & Williamson,* 529 U.S. at 143, 120 S.Ct. 1291 ("The 'classic judicial task of reconciling many laws enacted over time, and getting them to "make sense" in combination, necessarily assumes that the implications of a statute may be altered by the implications of a later statute.' ") (quoting *United States v. Fausto,* 484 U.S. 439, 453, 108 S.Ct. 668, 98 L.Ed.2d 830 (1988)).

39 *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc.,* 447 U.S. 102, 117, 100 S.Ct. 2051, 64 L.Ed.2d 766 (1980)

(quoting *United States v. Price,* 361 U.S. 304, 313, 80 S.Ct. 326, 4 L.Ed.2d 334 (1960)) (giving little weight to post-enactment legislative history in the interpretation of a statute); *see also United States v. United Mine Workers of Am.,* 330 U.S. 258, 281–82, 67 S.Ct. 677, 91 L.Ed. 884 (1947) (holding that statements of senators debating a 1943 amendment to a 1932 act "cannot [be] accept[ed] ... as authoritative guides to the construction of" the 1932 act where "some of [the senators] were not members of the Senate in 1932," because "[w]e fail to see how the remarks of these Senators in 1943 can serve to change the legislative intent of Congress expressed in 1932"); *South Carolina v. Regan,* 465 U.S. 367, 378 n. 17, 104 S.Ct. 1107, 79 L.Ed.2d 372 (1984) ("reject[ing]" any suggestion that the interpretation of a prior statute can be informed by "the committee reports that accompany subsequent legislation").

40 *Cf. I.N.S. v. Chadha,* 462 U.S. 919, 951, 103 S.Ct. 2764, 77 L.Ed.2d 317 (1983) (holding that Congressional action must satisfy bicameralism and presentment requirements, which "represent[ ] the Framers' decision that the legislative power of the Federal government be exercised in accord with a single, finely wrought and exhaustively considered, procedure").

41 The intent to amend the FDCA was explicit, for Congress dubbed FDAMA "An Act to amend the Federal Food, Drug, and Cosmetic Act [(FDCA)] and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes." Pub.L. No. 105–115, 111 Stat. 2296 (1997).

42 The Ninth Circuit worried, in contrast to *Koog,* that "Congress may have intended the original provisions of the FDCA to be severable, but meant for FDAMA's provisions to stand or fall together." *W. States,* 238 F.3d at 1098. That is an unlikely assumption. Congress amended an Act that contained an obvious and explicit severability provision, and it made plain its intention that FDAMA amendment be made part of the original Act (and codified in the Act as § 353a). If Congress had intended for the newly-added § 353a, and only § 353a, to be non-severable, it presumably would have said so.

43 Indeed, the Supreme Court recognized this consequence in reaching its decision that FDAMA's advertising provision was more restrictive than necessary to advance the government's interests and thus violated the final prong of the *Central Hudson,* 447 U.S. 557, 566, 100 S.Ct. 2343, 65 L.Ed.2d 341 (1980), test for regulation of commercial speech:

> Several non-speech-related means of drawing a line between compounding and large-scale manufacturing might be possible here.... It might even be sufficient to rely solely on the non-speech-related provisions of FDAMA, such as the requirement that compounding only be conducted in response to a prescription or a history of receiving a prescription, 21 U.S.C. § 353a(a), and the limitation on the percentage of a pharmacy's total sales that out-of-state sales of compounded drugs may represent, § 353a(b)(3)(B).... Nowhere in the legislative history of FDAMA or petitioners' briefs is there any explanation of why the Government believed forbidding advertising was a necessary as opposed to merely convenient means of achieving its interests.

W. States, 535 U.S. at 372–73, 122 S.Ct. 1497.

44 *See, e.g., New York v. United States,* 505 U.S. 144, 186–87, 112 S.Ct. 2408, 120 L.Ed.2d 120 (1992) (severing statute where invalid provision was one of multiple provisions designed to give states incentive to become self-sufficient in disposal of radioactive waste); *Koog,* 79 F.3d at 462–63 (severing statute where invalid provision was one of multiple provisions designed to regulate firearms purchases).

45 The requirements in the originally-proposed bill were much slimmer than those in the enacted version. The operative portion of the proposed bill required only that the drug be "compounded by a licensed pharmacist on the order of a licensed physician." H.R. 3199, 104th Cong.2d Sess. § 18 (1996).

46 Section 355 states,

> (a) Necessity of effective approval of application
> No person shall introduce or deliver for introduction into interstate commerce any *new drug,* unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

§ 355(a) (2000) (emphasis added).

47 S. Comm. on Labor and Human Resources, Food and Drug Administration Modernization and Accountability Act of 1997, S.Rep. No. 105–43, at 67 (1997).

48 Section 351(a)(5) of the FDCA deems an animal drug "adulterated" if it is a "new animal drug which is unsafe." Section 360b(a)(1) defines a "unsafe" animal drug as any "new animal drug" that has not received FDA approval. A animal drug is thus adulterated and unsafe if it is a "new animal drug" that has not received FDA approval.

49 Section 352(f) of the FDCA deems any drug to be "misbranded" if its label lacks "adequate directions for use." An FDA regulation, 21 C.F.R. § 201.122 (2008), exempts from the misbranding requirement bulk drugs used to manufacture

other animal drugs, so long as the finished product is not a unapproved "new drug." But if the drug created from the bulk drugs constitutes an unapproved "new drug," it is "misbranded" unless it bears "adequate directions for use."

50 *See Algon Chem.,* 879 F.2d at 1158; *9/1 Kg. Containers,* 854 F.2d at 178. The Third and Seventh Circuits held that compounded drugs from bulk suppliers constitute "new animal drugs." The district court sought to distinguish those cases by reasoning that unlike bulk drug suppliers and veterinarians, pharmacies compounding drugs from "legal bulk materials" fall outside the "new animal drug" definition. That distinction between traditional compounding and large-scale manufacturing, however, has no basis in the text of the FDCA's "new animal drug" definition.

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122 S.Ct. 1497
Supreme Court of the United States

Tommy G. THOMPSON, Secretary of Health and Human Services, et al., Petitioners,
v.
WESTERN STATES MEDICAL CENTER et al.

No. 01-344.
|
Argued Feb. 26, 2002.
|
Decided April 29, 2002.

Licensed pharmacies brought action challenging provisions of Food and Drug Administration Modernization Act (FDAMA) that prohibited advertising and promotion of particular compounded drugs. The United States District Court for the District of Nevada, David A. Ezra, J., 69 F.Supp.2d 1288, entered judgment in favor of the pharmacies, and government appealed. The Court of Appeals for the Ninth Circuit, 238 F.3d 1090, affirmed in part and reversed in part. Certiorari was granted. The Supreme Court, Justice O'Connor, held that provisions were unconstitutional restrictions of commercial speech.

Affirmed.

Justice Thomas concurred and filed opinion.

Justice Breyer dissented and filed opinion in which Justices Stevens, Ginsburg, and Chief Justice Rehnquist joined.

West Headnotes (5)

[1] **Constitutional Law** What Is "Commercial Speech"
Constitutional Law Trade or Business
Constitutional Law Health Care
Health Advertising and Other Representations
92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(A) In General
92XVIII(A)2 Commercial Speech in General
92k1536 What Is "Commercial Speech"
(Formerly 92k90.2)
92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(C) Trade or Business
92k1600 In General
(Formerly 92k90.2)
92 Constitutional Law

92XVIII Freedom of Speech, Expression, and Press
92XVIII(E) Advertising and Signs
92XVIII(E)2 Advertising
92k1647 Health Care
(Formerly 92k90.3)
198H Health
198HI Regulation in General
198HI(E) Drugs;Medical Devices and Instruments
198Hk308 Advertising and Other Representations
(Formerly 198Hk198, 138k16 Drugs and Narcotics)

Soliciting of prescriptions for particular compounded drugs and advertising of such drugs, as prohibited by the Food and Drug Administration Modernization Act (FDAMA), constituted "commercial speech" for purposes of the First Amendment. U.S.C.A. Const.Amend. 1; Federal Food, Drug, and Cosmetic Act, § 503A(a, c), as amended, 21 U.S.C.A. § 353a(a, c).

42 Cases that cite this headnote

[2] **Constitutional Law** Commercial Speech in General

92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(A) In General
92XVIII(A)2 Commercial Speech in General
92k1535 In General
(Formerly 92k90.2)

Not all regulation of commercial speech is unconstitutional. U.S.C.A. Const.Amend. 1.

30 Cases that cite this headnote

[3] **Constitutional Law** Reasonableness;Relationship to Governmental Interest

92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(A) In General
92XVIII(A)2 Commercial Speech in General
92k1541 Reasonableness;Relationship to Governmental Interest
(Formerly 92k90.2)

Under *Central Hudson*, commercial speech that neither concerns unlawful activity nor is misleading may be regulated if: asserted governmental interest is substantial; regulation directly advances that interest; and regulation is not more extensive than is necessary to serve that interest. (Per Justice O'Connor, with three Justices concurring and one Justice concurring separately). U.S.C.A. Const.Amend. 1.

70 Cases that cite this headnote

[4] **Constitutional Law** Trade or Business

Constitutional Law Health Care

Health Validity

92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(C) Trade or Business
92k1600 In General
(Formerly 92k90.2)

92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(E) Advertising and Signs
92XVIII(E)2 Advertising
92k1647 Health Care
(Formerly 92k90.3)
198H Health
198HI Regulation in General
198HI(A) In General
198Hk102 Constitutional and Statutory Provisions
198Hk105 Validity
(Formerly 198Hk198, 138k16 Drugs and Narcotics)

Provisions of Food and Drug Administration Modernization Act (FDAMA) that exempted compounded drugs from Food and Drug Administration's drug approval requirements if providers of such drugs refrained from advertising, promoting, or soliciting prescriptions for particular compounded drugs were unconstitutional restrictions of commercial speech. U.S.C.A. Const.Amend. 1; Federal Food, Drug, and Cosmetic Act, § 503A(a, c), as amended, 21 U.S.C.A. § 353a(a, c).

33 Cases that cite this headnote

[5] **Constitutional Law** Commercial Speech in General

92 Constitutional Law
92XVIII Freedom of Speech, Expression, and Press
92XVIII(A) In General
92XVIII(A)2 Commercial Speech in General
92k1535 In General
(Formerly 92k90.2)

Party seeking to uphold a restriction on commercial speech carries the burden of justifying it. U.S.C.A. Const.Amend. 1.

31 Cases that cite this headnote

West Codenotes

Held Unconstitutional
21 U.S.C. § 353a

****1498 *357** *Syllabus* [*]

[*] The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States v. Detroit Timber & Lumber Co.,* 200 U.S. 321, 337, 26 S.Ct. 282, 50 L.Ed. 499.

Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to an individual patient's needs. The Food and Drug Administration Modernization Act of 1997 (FDAMA) exempts "compounded drugs" from the Food and Drug Administration's (FDA) standard drug approval requirements under the Federal Food, Drug, and Cosmetic Act (FDCA), so long as the providers of the compounded drugs abide by several restrictions, including that the prescription be "unsolicited," 21 U.S.C. § 353a(a), and that the providers "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," § 353a(c). Respondents, a group of licensed pharmacies that specialize in compounding drugs, sought to enjoin

enforcement of the advertising and solicitation provisions, arguing that they violate the First Amendment's free speech guarantee. The District Court agreed and granted respondents summary judgment, holding that the provisions constitute unconstitutional restrictions on commercial speech under *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N. Y.,* 447 U.S. 557, 566, 100 S.Ct. 2343, 65 L.Ed.2d 341. Affirming in relevant part, the Ninth Circuit held that the restrictions in question fail *Central Hudson's* test because the Government had not demonstrated that the restrictions would directly advance its interests or that alternatives less restrictive of speech were unavailable.

Held: The FDAMA's prohibitions on soliciting prescriptions for, and advertising, compounded drugs amount to unconstitutional restrictions on commercial speech. Pp. 1503-1509.

(a) For a commercial speech regulation to be constitutionally permissible under the *Central Hudson* test, the speech in question must concern lawful activity and not be misleading, the asserted governmental interest to be served by the regulation must be substantial, and the regulation must "directly advanc [e]" the governmental interest and "not [be] more extensive than is necessary to serve that interest," 447 U.S., at 566, 100 S.Ct. 2343. Pp. 1503-1504.

(b) The Government asserts that three substantial interests underlie the FDAMA: (1) preserving the effectiveness and integrity of the ***358** FDCA's new drug approval process and the protection of the public health it provides; (2) preserving the availability of compounded drugs for patients who, for particularized medical reasons, cannot use commercially available products approved by the FDA; and (3) achieving the proper balance between those two competing interests. Preserving the new drug approval process is clearly an important governmental interest, as is permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. Because pharmacists do not make enough money from ****1499** small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, however, it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the entire new drug approval process. The Government therefore needs to be able to draw a line between small-scale compounding and large-scale drug manufacturing. The Government argues that the FDAMA's speech-related provisions provide just such a line: As long as pharmacists do not advertise particular compounded drugs, they may sell compounded drugs without first undergoing safety and efficacy testing and obtaining FDA approval. However, even assuming that the FDAMA's prohibition on advertising compounded drugs "directly advance[s]" the Government's asserted interests, the Government has failed to demonstrate that the speech restrictions are "not more extensive than is necessary to serve [those] interest[s]." *Central Hudson, supra,* at 566, 100 S.Ct. 2343. If the Government can achieve its interests in a manner that does not restrict commercial speech, or that restricts less speech, the Government must do so. *E.g., Rubin v. Coors Brewing Co.,* 514 U.S. 476, 490-491, 115 S.Ct. 1585, 131 L.Ed.2d 532. Several non-speech-related means of drawing a line between compounding and large-scale manufacturing might be possible here. For example, the Government could ban the use of commercial scale manufacturing or testing equipment in compounding drug products, prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received, or prohibit them from offering compounded drugs at wholesale to other state licensed persons or commercial entities for resale. The Government has not offered any reason why such possibilities, alone or in combination, would be insufficient to prevent compounding from occurring on such a scale as to undermine the new drug approval process. Pp. 1504-1507.

(c) Even if the Government had argued (as does the dissent) that the FDAMA's speech-related restrictions were motivated by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway, that fear would fail to justify the restrictions. This ***359** concern rests on the questionable assumption that doctors would prescribe unnecessary medications and amounts to a fear that people would make bad decisions if given truthful information, a notion that the Court rejected as a justification for an advertising ban in, *e.g., Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.,* 425 U.S. 748, 770, 96 S.Ct. 1817, 48 L.Ed.2d 346. Pp. 1507-1508.

(d) If the Government's failure to justify its decision to regulate speech were not enough to convince the Court that the FDAMA's advertising provisions were unconstitutional, the amount of beneficial speech prohibited by the FDAMA would be. Forbidding the advertisement of compounded drugs would prevent pharmacists with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding. For example, a pharmacist serving a children's hospital where many patients are unable to swallow pills would be prevented from telling the children's doctors about a new development in compounding that allowed a drug that was previously available only in pill form to be administered another way. The fact that the FDAMA would prohibit such seemingly useful speech even though doing so does not appear to directly further any asserted governmental objective confirms that the prohibition is unconstitutional. Pp. 1508-1509.

238 F.3d 1090, affirmed.

O'CONNOR, J., delivered the opinion of the Court, in which SCALIA, KENNEDY, SOUTER, and THOMAS, **1500 JJ., joined. THOMAS, J., filed a concurring opinion, *post,* p. 1509. BREYER, J., filed a dissenting opinion, in which REHNQUIST, C.J., and STEVENS and GINSBURG, JJ., joined, *post,* p. 1509.

Attorneys and Law Firms

Edwin S. Kneedler, Washington, DC, for petitioners.

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Opinion

***360** Justice O'CONNOR delivered the opinion of the Court.

Section 127(a) of the Food and Drug Administration Modernization Act of 1997 (FDAMA or Act), 111 Stat. 2328, 21 U.S.C. § 353a, exempts "compounded drugs" from the Food and Drug Administration's standard drug approval requirements as long as the providers of those drugs abide by several restrictions, including that they refrain from advertising or promoting particular compounded drugs. Respondents, a group of licensed pharmacies that specialize in compounding drugs, sought to enjoin enforcement of the subsections of the Act dealing with advertising and solicitation, arguing that those provisions violate the First Amendment's free speech guarantee. The District Court agreed with respondents and granted their motion for summary judgment, holding that the provisions do not meet the test for acceptable government regulation of commercial speech set forth in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N. Y.,* 447 U.S. 557, 566, 100 S.Ct. 2343, 65 L.Ed.2d 341 (1980). The court invalidated the relevant provisions, severing them from the rest of § 127(a).

The Court of Appeals for the Ninth Circuit affirmed in part and reversed in part, agreeing that the provisions regarding advertisement and promotion are unconstitutional but finding them not to be severable from the rest of § 127(a). Petitioners challenged only the Court of Appeals' constitutional holding in their petition for certiorari, and respondents did not file a cross-petition. We therefore address only the constitutional question, having no occasion to review the Court of Appeals' severability determination. We conclude, as did the courts below, that § 127(a)'s provisions regarding advertisement and promotion amount to unconstitutional restrictions on commercial speech, and we therefore affirm.

I

Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create ***361** a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that

are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product. It is a traditional component of the practice of pharmacy, see J. Thompson, A Practical Guide to Contemporary Pharmacy Practice 11.3 (1998), and is taught as part of the standard curriculum at most pharmacy schools, see American Council on Pharmaceutical Education, Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree, Standard 10(a) (adopted June 14, 1997). Many States specifically regulate compounding practices as part of their regulation of pharmacies. See, *e.g.,* Cal.Code Regs., tit. 16, §§ 1716.2, 1751 (2002); Ind. Admin. Code, tit. 856, §§ 1-30-8, 1-30-18, 1-28-8 (2001); N.H.Code Admin. Rules Ann. Pharmacy, pts. PH 404, PH 702.01 (2002); 22 Tex. Admin. Code § 291.36 (2002). Some require all licensed pharmacies to offer compounding services. See, *e.g.,* 49 Pa.Code § 27.18(p)(2) (2002); W. Va.Code St. Rules, tit. 15, § 19.4 (2002). Pharmacists may provide compounded drugs to patients only upon receipt of a valid prescription ****1501** from a doctor or other medical practitioner licensed to prescribe medication. See, *e.g.,* Okla. Admin. Code §§ 535:15-10-3, 535:15-10-9(d) (2001); Colo. State Board of Pharmacy Rule 3.02.10 (2001).

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), 21 U.S.C. §§ 301-397, regulates drug manufacturing, marketing, and distribution. Section 505(a) of the FDCA, 52 Stat. 1052, as amended, 76 Stat. 784, provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed [with the Food and Drug Administration] is effective with respect to such drug." 21 U.S.C. § 355(a). "[N]ew drug" is defined by § 201(p)(1) of the FDCA, 52 Stat. 1041, as amended, 76 Stat. 781, as "[a]ny drug ... not ***362** generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 321(p). The FDCA invests the Food and Drug Administration (FDA) with the power to enforce its requirements. § 371(a).

For approximately the first 50 years after the enactment of the FDCA, the FDA generally left regulation of compounding to the States. Pharmacists continued to provide patients with compounded drugs without applying for FDA approval of those drugs. The FDA eventually became concerned, however, that some pharmacists were manufacturing and selling drugs under the guise of compounding, thereby avoiding the FDCA's new drug requirements. In 1992, in response to this concern, the FDA issued a Compliance Policy Guide, which announced that the "FDA may, in the exercise of its enforcement discretion, initiate federal enforcement actions ... when the scope and nature of a pharmacy's activities raises the kinds of concerns normally associated with a manufacturer and ... results in significant violations of the new drug, adulteration, or misbranding provisions of the Act." Compliance Policy Guide 7132.16 (hereinafter Guide), App. to Pet. for Cert. 76a. The Guide explained that the "FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner," and that such activity was not the subject of the Guide. *Id.,* at 71a. The Guide said, however, "that while retail pharmacies ... are exempted from certain requirements of the [FDCA], they are not the subject of any general exemption from the new drug, adulteration, or misbranding provisions" of the FDCA. *Id.,* at 72a. It stated that the "FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in ***363** manufacturing, distributing, and promoting unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that constitute violations of the [FDCA]." *Ibid.* The Guide expressed concern that drug products "manufactured and distributed in commercial amounts without [the] FDA's prior approval" could harm the public health. *Id.,* at 73a.

In light of these considerations, the Guide announced that it was FDA policy to permit pharmacists to compound drugs after receipt of a valid prescription for an individual patient or to compound drugs in "very limited quantities" before receipt of a valid prescription if they could document a history of receiving valid prescriptions "generated solely within an established professional practitioner-patient-pharmacy relationship" and if they maintained the prescription on file as required by state law. *Id.,* at 73a-75a. Compounding in such circumstances was permitted as long as the pharmacy's activities did not raise "the kinds of concerns normally associated with a manufacturer." *Id.,* at 76a. The Guide listed nine examples of activities that the FDA believed raised such concerns ****1502** and that would therefore be considered

by the agency in determining whether to bring an enforcement action. These activities included: "[s]oliciting business (*e.g.,* promoting, advertising, or using salespersons) to compound specific drug products, product classes, or therapeutic classes of drug products"; "[c]ompounding, regularly, or in inordinate amounts, drug products that are commercially available ... and that are essentially generic copies of commercially available, FDA-approved drug products"; using commercial scale manufacturing or testing equipment to compound drugs; offering compounded drugs at wholesale; and "[d]istributing inordinate amounts of compounded products out of state." *Id.,* at 76a-77a. The Guide further warned that pharmacies could not dispense drugs to third parties for resale to individual patients without losing their status as retail entities. *Id.,* at 75a.

***364** Congress turned portions of this policy into law when it enacted the FDAMA in 1997. The FDAMA, which amends the FDCA, exempts compounded drugs from the FDCA's "new drug" requirements and other requirements provided the drugs satisfy a number of restrictions. First, they must be compounded by a licensed pharmacist or physician in response to a valid prescription for an identified individual patient, or, if prepared before the receipt of such a prescription, they must be made only in "limited quantities" and in response to a history of the licensed pharmacist's or physician's receipt of valid prescription orders for that drug product within an established relationship between the pharmacist, the patient, and the prescriber. 21 U.S.C. § 353a(a). Second, the compounded drug must be made from approved ingredients that meet certain manufacturing and safety standards, §§ 353a(b)(1)(A)-(B), and the compounded drug may not appear on an FDA list of drug products that have been withdrawn or removed from the market because they were found to be unsafe or ineffective, § 353a(b)(1)(C). Third, the pharmacist or physician compounding the drug may not "compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product." § 353a(b)(1)(D). Fourth, the drug product must not be identified by the FDA as a drug product that presents demonstrable difficulties for compounding in terms of safety or effectiveness. § 353a(b)(3)(A). Fifth, in States that have not entered into a "memorandum of understanding" with the FDA addressing the distribution of "inordinate amounts" of compounded drugs in interstate commerce, the pharmacy, pharmacist, or physician compounding the drug may not distribute compounded drugs out of state in quantities exceeding five percent of that entity's total prescription orders. § 353a(b)(3)(B). Finally, and most relevant for this litigation, the prescription must be "unsolicited," § 353a(a), and the pharmacy, licensed pharmacist, or licensed physician ***365** compounding the drug may "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," § 353a(c). The pharmacy, licensed pharmacist, or licensed physician may, however, "advertise and promote the compounding service." *Ibid.*

Respondents are a group of licensed pharmacies that specialize in drug compounding. They have prepared promotional materials that they distribute by mail and at medical conferences to inform patients and physicians of the use and effectiveness of specific compounded drugs. Fearing that they would be prosecuted under the FDAMA if they continued to distribute those materials, respondents filed a complaint in the United States District Court for the District of Nevada, arguing that the Act's requirement that they refrain from advertising and promoting their products if they wish to continue compounding violates the Free Speech Clause of the First Amendment. Specifically, they challenged the requirement that prescriptions for compounded drugs be ****1503** "unsolicited," 21 U.S.C. § 353a(a), and the requirement that pharmacists "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," § 353a(c). The District Court granted summary judgment to respondents, finding that the FDAMA's speech-related provisions constitute unconstitutional restrictions on commercial speech under *Central Hudson,* 447 U.S., at 566, 100 S.Ct. 2343, and that their enforcement should therefore be enjoined. *Western States Medical Center v. Shalala,* 69 F.Supp.2d 1288 (D.Nev.1999). The District Court, however, found those provisions to be severable from the rest of § 127(a) of the FDAMA, 21 U.S.C. § 353a, and so left the Act's other compounding requirements intact.

The Government appealed both the holding that the speech-related provisions were unconstitutional and the holding that those provisions were severable from the rest of § 127(a). The Court of Appeals for the Ninth Circuit affirmed in part and reversed in part. *Western States Medical* ***366** *Center v. Shalala,* 238 F.3d 1090 (C.A.9 2001). The Court of Appeals agreed that the FDAMA's advertisement and solicitation restrictions fail *Central Hudson's* test for permissible regulation

of commercial speech, finding that the Government had not demonstrated that the speech restrictions would directly advance its interests or that alternatives less restrictive of speech were unavailable. The Court of Appeals disagreed, however, that the speech-related restrictions were severable from the rest of § 127(a), 21 U.S.C. § 353a, explaining that the FDAMA's legislative history demonstrated that Congress intended to exempt compounding from the FDCA's requirements only in return for a prohibition on promotion of specific compounded drugs. Accordingly, the Court of Appeals invalidated § 127(a) in its entirety.

We granted certiorari, 534 U.S. 992, 122 S.Ct. 457, 151 L.Ed.2d 375 (2001), to consider whether the FDAMA's prohibitions on soliciting prescriptions for, and advertising, compounded drugs violate the First Amendment. Because neither party petitioned for certiorari on the severability issue, we have no occasion to review that portion of the Court of Appeals' decision. Likewise, the provisions of the FDAMA outside § 127(a), which are unrelated to drug compounding, are not an issue here and so remain unaffected.

II

[1] The parties agree that the advertising and soliciting prohibited by the FDAMA constitute commercial speech. In *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.,* 425 U.S. 748, 96 S.Ct. 1817, 48 L.Ed.2d 346 (1976), the first case in which we explicitly held that commercial speech receives First Amendment protection, we explained the reasons for this protection: "It is a matter of public interest that [economic] decisions, in the aggregate, be intelligent and well-informed. To this end, the free flow of commercial information is indispensable." *Id.,* at 765, 96 S.Ct. 1817. Indeed, we recognized that a "particular consumer's interest in the free flow of commercial information ... may be as keen, if not keener by far, than ***367** his interest in the day's most urgent political debate." *Id.,* at 763, 96 S.Ct. 1817. We have further emphasized:

> "The commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. Some of the ideas and information are vital, some of slight worth. But the general rule is that the speaker and the audience, not the government, assess the value of the information presented. Thus, even a communication that does no more than propose a commercial transaction is entitled to the coverage of the First Amendment." *Edenfield v. Fane,* 507 U.S. 761, 767, 113 S.Ct. 1792, 123 L.Ed.2d 543 (1993).

[2] **[3]** Although commercial speech is protected by the First Amendment, not all ****1504** regulation of such speech is unconstitutional. See *Virginia Bd. of Pharmacy, supra,* at 770, 96 S.Ct. 1817. In *Central Hudson, supra,* we articulated a test for determining whether a particular commercial speech regulation is constitutionally permissible. Under that test we ask as a threshold matter whether the commercial speech concerns unlawful activity or is misleading. If so, then the speech is not protected by the First Amendment. If the speech concerns lawful activity and is not misleading, however, we next ask "whether the asserted governmental interest is substantial." *Id.,* at 566, 100 S.Ct. 2343. If it is, then we "determine whether the regulation directly advances the governmental interest asserted," and, finally, "whether it is not more extensive than is necessary to serve that interest." *Ibid.* Each of these latter three inquiries must be answered in the affirmative for the regulation to be found constitutional.

Neither party has challenged the appropriateness of applying the *Central Hudson* framework to the speech-related provisions at issue here. Although several Members of the Court have expressed doubts about the *Central Hudson* analysis and whether it should apply in particular cases, see, *e.g., Greater New Orleans Broadcasting Assn., Inc. v.* ***368** *United States,* 527 U.S. 173, 197, 119 S.Ct. 1923, 144 L.Ed.2d 161 (1999) (THOMAS, J., concurring in judgment*); 44 Liquormart, Inc. v. Rhode Island,* 517 U.S. 484, 501, 510-514, 116 S.Ct. 1495, 134 L.Ed.2d 711 (1996) (opinion of STEVENS, J., joined by KENNEDY and GINSBURG, JJ.); *id.,* at 517, 116 S.Ct. 1495 (SCALIA, J., concurring in part and concurring in judgment); *id.,* at 518, 116 S.Ct. 1495 (THOMAS, J., concurring in part and concurring in judgment), there is no need in this case to break new ground. " '*Central Hudson,* as applied in our more recent commercial speech

cases, provides an adequate basis for decision.' " *Lorillard Tobacco Co. v. Reilly,* 533 U.S. 525, 554-555, 121 S.Ct. 2404, 150 L.Ed.2d 532 (2001) (quoting *Greater New Orleans, supra,* at 184, 119 S.Ct. 1923).

III

[4] The Government does not attempt to defend the FDAMA's speech-related provisions under the first prong of the *Central Hudson* test; *i.e.,* it does not argue that the prohibited advertisements would be about unlawful activity or would be misleading. Instead, the Government argues that the FDAMA satisfies the remaining three prongs of the *Central Hudson* test.

The Government asserts that three substantial interests underlie the FDAMA. The first is an interest in "preserv[ing] the effectiveness and integrity of the FDCA's new drug approval process and the protection of the public health that it provides." Brief for Petitioners 19. The second is an interest in "preserv[ing] the availability of compounded drugs for those individual patients who, for particularized medical reasons, cannot use commercially available products that have been approved by the FDA." *Id.,* at 19-20. Finally, the Government argues that "[a]chieving the proper balance between those two independently compelling but competing interests is itself a substantial governmental interest." *Id.,* at 20.

Explaining these interests, the Government argues that the FDCA's new drug approval requirements are critical to the public health and safety. It claims that the FDA's ***369** experience with drug regulation demonstrates that proof of the safety and effectiveness of a new drug needs to be established by rigorous, scientifically valid clinical studies because impressions of individual doctors, who cannot themselves compile sufficient safety data, cannot be relied upon. The Government also argues that a premarket approval process, under which manufacturers are required to put their proposed drugs through tests of safety and effectiveness in order to obtain FDA approval to market the drugs, is ****1505** the best way to guarantee drug safety and effectiveness.

While it praises the FDCA's new drug approval process, the Government also acknowledges that "because obtaining FDA approval for a new drug is a costly process, requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment." *Id.,* at 26. The Government argues that eliminating the practice of compounding drugs for individual patients would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages.

Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from ***370** small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs. Given this, the Government needs to be able to draw a line between small-scale compounding and large-scale drug manufacturing. That line must distinguish compounded drugs produced on such a small scale that they could not undergo safety and efficacy testing from drugs produced and sold on a large enough scale that they could undergo such testing and therefore must do so.

The Government argues that the FDAMA's speech-related provisions provide just such a line, *i.e.,* that, in the terms of *Central Hudson,* they "directly advanc[e] the governmental interest[s] asserted." 447 U.S., at 566, 100 S.Ct. 2343. Those provisions use advertising as the trigger for requiring FDA approval-essentially, as long as pharmacists do not

advertise particular compounded drugs, they may sell compounded drugs without first undergoing safety and efficacy testing and obtaining FDA approval. If they advertise their compounded drugs, however, FDA approval is required. The Government explains that traditional (or, in its view, desirable) compounding responds to a physician's prescription and an individual patient's particular medical situation, and that "[a]dvertising the particular products created in the provision of [such] service (as opposed to advertising the compounding service itself) is not necessary to ... this type of responsive and customized service." Brief for Petitioners 34. The Government argues that advertising particular products is useful in a broad market but is not useful when particular products are designed in response to an individual's "often unique need[s]." *Ibid.* The Government contends that, because of this, advertising is not typically associated with compounding for particular individuals. In contrast it is typically associated, the Government claims, with large-scale production of a drug for a substantial market. The Government argues that advertising, ***371** therefore, is "a fair proxy for actual or intended large-scale manufacturing," and that Congress' decision to limit the FDAMA's compounding exemption to pharmacies that do not engage in promotional activity was "rationally calculated" to avoid creating " 'a loophole that would allow unregulated drug manufacturing to occur under the guise of pharmacy compounding.' " *Id.,* at 35 (quoting ****1506** 143 Cong. Rec. S9839 (Sept. 24, 1997) (statement of Sen. Kennedy)).

The Government seems to believe that without advertising it would not be possible to market a drug on a large enough scale to make safety and efficacy testing economically feasible. The Government thus believes that conditioning an exemption from the FDA approval process on refraining from advertising is an ideal way to permit compounding and yet also guarantee that compounding is not conducted on such a scale as to undermine the FDA approval process. Assuming it is true that drugs cannot be marketed on a large scale without advertising, the FDAMA's prohibition on advertising compounded drugs might indeed "directly advanc[e]" the Government's interests. *Central Hudson,* 447 U.S., at 566, 100 S.Ct. 2343. Even assuming that it does, however, the Government has failed to demonstrate that the speech restrictions are "not more extensive than is necessary to serve [those] interest[s]." *Ibid.* In previous cases addressing this final prong of the *Central Hudson* test, we have made clear that if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so. In *Rubin v. Coors Brewing Co.,* 514 U.S. 476, 115 S.Ct. 1585, 131 L.Ed.2d 532 (1995), for example, we found a law prohibiting beer labels from displaying alcohol content to be unconstitutional in part because of the availability of alternatives "such as directly limiting the alcohol content of beers, prohibiting marketing efforts emphasizing high alcohol strength ..., or limiting the labeling ban only to malt liquors." *Id.,* at 490-491, 115 S.Ct. 1585. The fact that "all of [these alternatives] could advance the Government's asserted interest ***372** in a manner less intrusive to ... First Amendment rights" indicated that the law was "more extensive than necessary." *Id.,* at 491, 115 S.Ct. 1585. See also *44 Liquormart, Inc. v. Rhode Island,* 517 U.S., at 507, 116 S.Ct. 1495 (plurality opinion) (striking down a prohibition on advertising the price of alcoholic beverages in part because "alternative forms of regulation that would not involve any restriction on speech would be more likely to achieve the State's goal of promoting temperance").

Several non-speech-related means of drawing a line between compounding and large-scale manufacturing might be possible here. First, it seems that the Government could use the very factors the FDA relied on to distinguish compounding from manufacturing in its 1992 Guide. For example, the Government could ban the use of "commercial scale manufacturing or testing equipment for compounding drug products." Guide, App. to Pet. for Cert. 76a. It could prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received. See *ibid.* It could prohibit pharmacists from "[o]ffering compounded drug products at wholesale to other state licensed persons or commercial entities for resale." *Id.,* at 77a. Alternately, it could limit the amount of compounded drugs, either by volume or by numbers of prescriptions, that a given pharmacist or pharmacy sells out of state. See *ibid.* Another possibility not suggested by the Guide would be capping the amount of any particular compounded drug, either by drug volume, number of prescriptions, gross revenue, or profit that a pharmacist or pharmacy may make or sell in a given period of time. It might even be sufficient to rely solely on the non-speech-related provisions of the FDAMA, such as the requirement that compounding only be conducted in response to a prescription or a history of receiving a prescription, 21 U.S.C. § 353a(a), and the limitation on the percentage of a pharmacy's total sales that out-of-state sales of compounded drugs may represent, § 353a(b)(3)(B).

[5] ***373** The Government has not offered any reason why these possibilities, alone or in combination, would be insufficient to ****1507** prevent compounding from occurring on such a scale as to undermine the new drug approval process. Indeed, there is no hint that the Government even considered these or any other alternatives. Nowhere in the legislative history of the FDAMA or petitioners' briefs is there any explanation of why the Government believed forbidding advertising was a necessary as opposed to merely convenient means of achieving its interests. Yet "[i]t is well established that 'the party seeking to uphold a restriction on commercial speech carries the burden of justifying it.' " *Edenfield v. Fane,* 507 U.S., at 770, 113 S.Ct. 1792 (quoting *Bolger v. Youngs Drug Products Corp.,* 463 U.S. 60, 71, n. 20, 103 S.Ct. 2875, 77 L.Ed.2d 469 (1983)). The Government simply has not provided sufficient justification here. If the First Amendment means anything, it means that regulating speech must be a last-not first-resort. Yet here it seems to have been the first strategy the Government thought to try.

The dissent describes another governmental interest-an interest in prohibiting the sale of compounded drugs to "patients who may not clearly need them," *post,* at 1510 (opinion of BREYER, J.)-and argues that "Congress could ... conclude that the advertising restrictions 'directly advance' " that interest, *post,* at 1513. Nowhere in its briefs, however, does the Government argue that this interest motivated the advertising ban. Although, for the reasons given by the dissent, Congress conceivably could have enacted the advertising ban to advance this interest, we have generally only sustained statutes on the basis of hypothesized justifications when reviewing statutes merely to determine whether they are rational. See L. Tribe, American Constitutional Law 1444-1446 (2d ed.1988) (describing the "rational basis" or "conceivable basis" test); see also, *e.g., Minnesota v. Clover Leaf Creamery Co.,* 449 U.S. 456, 466, 101 S.Ct. 715, 66 L.Ed.2d 659 (1981) (sustaining a milk packaging regulation under the "rational basis" test ***374** because "the Minnesota Legislature could rationally have decided that [the regulation] might foster greater use of environmentally desirable alternatives" (emphasis deleted)). The *Central Hudson* test is significantly stricter than the rational basis test, however, requiring the Government not only to identify specifically "a substantial interest to be achieved by [the] restrictio[n] on commercial speech," 447 U.S., at 564, 100 S.Ct. 2343, but also to prove that the regulation "directly advances" that interest and is "not more extensive than is necessary to serve that interest," *id.,* at 566, 100 S.Ct. 2343. The Government has not met any of these requirements with regard to the interest the dissent describes.

Even if the Government had argued that the FDAMA's speech-related restrictions were motivated by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway, that fear would fail to justify the restrictions. Aside from the fact that this concern rests on the questionable assumption that doctors would prescribe unnecessary medications (an assumption the dissent is willing to make based on one magazine article and one survey, *post,* at 1512, neither of which was relied upon by the Government), this concern amounts to a fear that people would make bad decisions if given truthful information about compounded drugs. See *supra,* at 1504 (explaining that the Government does not claim the advertisements forbidden by the FDAMA would be false or misleading). We have previously rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information. In *Virginia Bd. of Pharmacy,* the State feared that if people received price advertising from pharmacists, they would "choose the low-cost, low-quality service and drive the 'professional' pharmacist out ****1508** of business" and would "destroy the pharmacist-customer relationship" by going from one ***375** pharmacist to another. We found these fears insufficient to justify a ban on such advertising. 425 U.S., at 769, 96 S.Ct. 1817. We explained:

> "There is, of course, an alternative to this highly paternalistic approach. That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.... But the choice among these alternative approaches is not ours to make or the Virginia General Assembly's. It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us. Virginia is free to require whatever professional standards it wishes of its pharmacists; it may subsidize them or protect them from competition in other ways.... But it may not

do so by keeping the public in ignorance of the entirely lawful terms that competing pharmacists are offering." *Id.,* at 770, 96 S.Ct. 1817 (citation omitted).

See also *44 Liquormart, Inc. v. Rhode Island,* 517 U.S., at 503, 116 S.Ct. 1495 ("[B]ans against truthful, nonmisleading commercial speech ... usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth.... The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good" (citation omitted)).

Even if the Government had asserted an interest in preventing people who do not need compounded drugs from obtaining those drugs, the statute does not directly advance that interest. The dissent claims that the Government "must exclude from the area of permitted drug sales ... those compounded drugs sought by patients who may not ***376** clearly need them." *Post,* at 1510. Yet the statute does not directly forbid such sales. It instead restricts advertising, of course not just to those who do not need compounded drugs, but also to individuals who do need compounded drugs and their doctors. Although the advertising ban may reduce the demand for compounded drugs from those who do not need the drugs, it does nothing to prevent such individuals from obtaining compounded drugs other than requiring prescriptions. But if it is appropriate for the statute to rely on doctors to refrain from prescribing compounded drugs to patients who do not need them, it is not clear why it would not also be appropriate to rely on doctors to refrain from prescribing compounded drugs to patients who do not need them in a world where advertising was permitted.

The dissent may also be suggesting that the Government has an interest in banning the advertising of compounded drugs because patients who see such advertisements will be confused about the drugs' risks. See *post,* at 1514 ("[The Government] fears the systematic effect ... of advertisements that will not fully explain the complicated risks at issue"). This argument is precluded, however, by the fact that the Government does not argue that the advertisements are misleading. Even if the Government did argue that it had an interest in preventing misleading advertisements, this interest could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown.

If the Government's failure to justify its decision to regulate speech were not enough to convince us that the FDAMA's advertising provisions were unconstitutional, the amount of beneficial speech prohibited by the FDAMA would be. Forbidding the advertisement of compounded drugs would affect pharmacists other than ****1509** those interested in producing drugs on a large scale. It would prevent pharmacists ***377** with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding. For example, a pharmacist serving a children's hospital where many patients are unable to swallow pills would be prevented from telling the children's doctors about a new development in compounding that allowed a drug that was previously available only in pill form to be administered another way. Forbidding advertising of particular compounded drugs would also prohibit a pharmacist from posting a notice informing customers that if their children refuse to take medications because of the taste, the pharmacist could change the flavor, and giving examples of medications where flavoring is possible. The fact that the FDAMA would prohibit such seemingly useful speech even though doing so does not appear to directly further any asserted governmental objective confirms our belief that the prohibition is unconstitutional.

Accordingly, we affirm the Court of Appeals' judgment that the speech-related provisions of FDAMA § 127(a) are unconstitutional.

So ordered.

Justice THOMAS, concurring.

I concur because I agree with the Court's application of the test set forth in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N. Y.,* 447 U.S. 557, 100 S.Ct. 2343, 65 L.Ed.2d 341 (1980). I continue, however, to adhere to my view that cases such as this should not be analyzed under the *Central Hudson* test. "I do not believe that such a test should be applied to a restriction of 'commercial' speech, at least when, as here, the asserted interest is one that is to be achieved through keeping would-be recipients of the speech in the dark." *44 Liquormart, Inc. v. Rhode Island,* 517 U.S. 484, 523, 116 S.Ct. 1495, 134 L.Ed.2d 711 (1996) (opinion concurring in part and concurring in judgment).

***378** Justice BREYER, with whom THE CHIEF JUSTICE, Justice STEVENS, and Justice GINSBURG join, dissenting.

Federal law requires strict safety and efficacy testing of all "new" prescription "drugs." 21 U.S.C. § 355. See 21 CFR § 310.3(h) (2002) (defining "new drug" broadly). This testing process requires for every "new drug" a preclinical investigation and three separate clinical tests, including small, controlled studies of healthy and diseased humans as well as scientific double-blind studies designed to identify any possible health risk or side effect associated with the new drug. Practical Guide to Food and Drug Law and Regulation 95-102 (K. Piña & W. Pines eds.1998). The objective of this elaborate and time-consuming regulatory regime is to identify those health risks-both large and small-that a doctor or pharmacist might not otherwise notice.

At the same time, the law exempts from its testing requirements prescription drugs produced through "compounding"-a process "by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient." *Ante,* at 1500. The exemption is available, however, only if the pharmacist meets certain specified conditions, including the condition that the pharmacist not "advertise or promote the compounding of any *particular* drug." 21 U.S.C. § 353a(c) (emphasis added).

The Court holds that this condition restricts "commercial speech" in violation of the First Amendment. See *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N. Y.,* 447 U.S. 557, 564, 100 S.Ct. 2343, 65 L.Ed.2d 341 (1980). It concedes that the statutory provision tries to "[p]reserv[e] the effectiveness and integrity of the ... new drug approval process," *ante,* at 1505, and it assumes without deciding that the statute might " 'directly ****1510** advance' " that interest, *ante,* at 1506. It nonetheless finds the statute unconstitutional because it could advance that interest in other, less restrictive ways. *Ante,* at 1506-1507. I disagree with this conclusion, and I believe that the Court ***379** seriously undervalues the importance of the Government's interest in protecting the health and safety of the American public.

I

In my view, the advertising restriction "directly advances" the statute's important safety objective. That objective, as the Court concedes, is to confine the sale of untested, compounded, drugs to where they are medically needed. But to do so the statute must exclude from the area of permitted drug sales *both* (1) those drugs that traditional drug manufacturers might supply after testing-typically drugs capable of being produced in large amounts, *and* (2) those compounded drugs sought by patients who may not clearly need them-including compounded drugs produced in small amounts.

The majority's discussion focuses upon the first exclusionary need, but it virtually ignores the second. It describes the statute's objective simply as drawing a "line" that will "*distinguish* compounded drugs produced on such a *small scale* that they could not undergo safety and efficacy testing *from* drugs produced and sold on a *large* enough *scale* that they could undergo such testing and therefore must do so." *Ante,* at 1505 (emphasis added). This description overlooks the need for a second line-a line that will *distinguish* (1) sales of compounded drugs to those who clearly need them from (2) sales of compounded drugs to those for whom a specially tailored but untested drug is a convenience but not a medical necessity. That is to say, the statute, in seeking to confine distribution of untested tailored drugs, must look both at the amount supplied (to help decide whether ordinary manufacturers might provide a tested alternative) and at the nature of

demand (to help separate genuine need from simple convenience). Cf. 143 Cong. Rec. S9840 (Sept. 24, 1997) (remarks of Sen. Kennedy) (understanding that "some of the conditions are intended to ensure that the volume of compounding does not approach that ordinarily associated ***380** with drug manufacturing" while others are "intended to ensure that the compounded drugs that qualify for the exemption have appropriate assurances of quality and safety since [they] would not be subject to the more comprehensive regulatory requirements that apply to manufactured drug products").

This second intermediate objective is logically related to Congress' primary end-the minimizing of safety risks. The statute's basic exemption from testing requirements inherently creates risks simply by placing untested drugs in the hands of the consumer. Where an individual has a specific medical need for a specially tailored drug those risks are likely offset. But where an untested drug is a convenience, not a necessity, that offset is unlikely to be present.

That presumably is why neither the Food and Drug Administration (FDA) nor Congress anywhere suggests that all that matters is the total *amount* of a particular drug's sales. That is why the statute's history suggests that the amount supplied is not the whole story. See S.Rep. No. 105-43, p. 67 (1997) (statute seeks to assure "continued availability of compounded drug products as a component of *individualized* therapy, ... while ... prevent[ing] *small-scale* manufacturing under the guise of compounding" (emphasis added)); accord, H.R. Conf. Rep. No. 105-399, p. 94 (1997), U.S.Code Cong. & Admin.News 1997, pp. 2880, 2884. That is why the statute itself, as well as the FDA policy that the statute reflects, lists several distinguishing factors, of which advertising is one. See FDA Compliance Policy Guide 7132.16, reprinted in App. to Pet. ****1511** for Cert. 71a-77a (hereinafter Compliance Policy Guide). And that is likely why, when faced with the possibility of severing the advertising restriction from the rest of the statute, the Government argued that the "other conditions in section 353a alone are inadequate to achieve Congress's desired balance among competing interests." See Brief for Appellants in No. 99-17424(CA9), p. 57. See also *id.,* at 55 (to nullify advertising restrictions would undermine " 'finely tuned balance' " achieved ***381** by requiring that "pharmacies refrain from promoting and soliciting prescriptions for particular compounded drug products until they have been proven safe and effective").

Ensuring that the risks associated with compounded drug prescriptions are offset by the benefits is also why public health authorities, testifying in Congress, insisted that the doctor's prescription represent an *individualized* determination of need. See, *e.g.,* FDA Reform Legislation: Hearings before the Subcommittee on Health and the Environment of the House Committee on Commerce, 104th Cong., 2d Sess., 120 (1996) (hereinafter FDA Reform Legislation) (statement of Mary K. Pendergast, Deputy Commissioner of the FDA and Senior Advisor to the Commissioner) (Allowing traditional compounding is "good medicine" because "an individual physician" was making "an individualized determination for a patient"). See also National Association of Boards of Pharmacy, Model State Pharmacy Act and Rules, Art. I, § 1.05(e) (1996) (hereinafter NABP Model Act) (defining "[c]ompounding" as involving a prescription "based on the Practitioner/patient/Pharmacist relationship in the course of professional practice").

And that, in part, is why federal and state authorities have long permitted pharmacists to advertise the fact that they compound drugs, while forbidding the advertisement of individual compounds. See Compliance Policy Guide 76a; Good Compounding Practices Applicable to State Licensed Pharmacies, NABP Model Act, App. C.2, subpart A (forbidding pharmacists to "solicit business (*e.g.,* promote, advertise, or use salespersons) to compound specific drug products"). The definitions of drug manufacturing and compounding used by the NABP and at least 13 States reflect similar distinctions. NABP Model Act, Art. I, §§ 105(e), (t), and (u) (defining drug manufacturing to "include the promotion and marketing of such drugs or devices" but excluding any reference to promotion or marketing from the definition of drug compounding); Alaska Stat. §§ 08.80.480(3) and (15) (2000) ***382** (same); La.Stat. Ann. §§ 37:1164(5) and (25) (West 2000) (same); Miss.Code Ann. §§ 73-21-73(c) and (s) (Lexis 1973-2000) (same); Mont.Code Ann. § 37-7-101(7) (1997) (same); N.H.Rev.Stat. Ann. §§ 318-1(III) and (VIII) (Supp.2001) (same); N.M. Stat. Ann. §§ 61-11-2(C) and (Q) (2001) (same); Ohio Rev.Code Ann. § 3715.01(14) (West Supp.2002) (same); Okla. Stat., Tit 59, §§ 353.1(20) and (26) (Supp.2002) (same); S.C.Code Ann. §§ 40-43-30(7) and (29) (2001) (same); Tenn.Code Ann. §§ 63-10-404(4) and (18) (1997) (same); Tex. Occ.Code Ann. §§ 551.003(9) and (23) (2002 Pamphlet) (same); W. Va.Code §§ 30-5-1b(c) and (*o*) (1966-1998) (same).

These policies and statutory provisions reflect the view that individualized consideration is more likely present, and convenience alone is more likely absent, when demand for a compounding prescription originates with a doctor, not an advertisement. The restrictions try to assure that demand is generated doctor-to-patient-to-pharmacist, not pharmacist-to-advertisement-to-patient-to-doctor. And they do so in order to diminish the likelihood that those who do not genuinely need untested compounded drugs will not receive them.

There is considerable evidence that the relevant means-the advertising restrictions-directly advance this statutory objective. No one denies that the FDA's complex testing system for new drugs-a system that typically relies upon double-blind or other scientific studies-is more ****1512** likely to find, and to assess, small safety risks than are physicians or pharmacists relying upon impressions and anecdotes. See *supra,* at 1509.

Nor can anyone deny that compounded drugs carry with them special risks. After all, compounding is not necessarily a matter of changing a drug's flavor, cf. *ante,* at 1509, but rather it is a matter of combining different ingredients in new, untested ways, say, adding a pain medication to an antihistamine to counteract allergies or increasing the ratio of approved ingredients in a salve to help the body absorb it ***383** at a faster rate. And the risks associated with the untested combination of ingredients or the quicker absorption rate or the working conditions necessary to change an old drug into its new form can, for some patients, mean infection, serious side effects, or even death. See, *e.g.,* J. Thompson, A Practical Guide to Contemporary Pharmacy Practice 11.5 (1998) (hereinafter Contemporary Pharmacy Practice). Cf. 21 CFR § 310.3(h)(1) (2002) (considering a drug to be "new" and subject to the approval process if the "substance which composes such drug" is new); § 310.3(h)(3) (considering a drug to be "new" and subject to the approval process if approved ingredients are combined in new proportions).

There is considerable evidence that consumer oriented advertising will create strong consumer-driven demand for a particular drug. See, *e.g.,* National Institute for Health Care Management, Factors Affecting the Growth of Prescription Drug Expenditures iii (July 9, 1999) (three antihistamine manufacturers spent $313 million on advertising in 1998 and accounted for 90% of prescription drug antihistamine market); Kritz, Ask Your Doctor About ... Which of the Many Advertised Allergy Drugs Are Right for You? Washington Post, June 6, 2000, Health, p. 9 (The manufacturer of the world's top selling allergy drug, the eighth best-selling drug in the United States, spent almost $140 million in 1999 on advertising); 1999 Prevention Magazine 10 (spending on direct-to-consumer advertising of prescription medicine increased from $965.2 million in 1997 to $1.33 billion in 1998).

And there is strong evidence that doctors will often respond affirmatively to a patient's request for a specific drug that the patient has seen advertised. See *id.,* at 32 (84% of consumers polled report that doctors accommodate their request for a specific drug); Henry J. Kaiser Family Foundation, Understanding the Effects of Direct-to-Consumer Prescription Drug Advertising 3 (Nov.2001) (A foundation survey found that more than one in eight Americans had asked ***384** for-and received-a specific prescription from their doctor in response to an advertisement).

In these circumstances, Congress could reasonably conclude that doctors will respond affirmatively to a patient's request for a compounded drug even if the doctor would not normally prescribe it. When a parent learns that a child's pill can be administered in liquid form, when a patient learns that a compounded skin cream has an enhanced penetration rate, or when an allergy sufferer learns that a compounded antiinflammatory/allergy medication can alleviate a sinus headache without the sedative effects of antihistamines, that parent or patient may well ask for the desired prescription. And the doctor may well write the prescription even in the absence of special need-at least if any risk likely to arise from lack of testing is so small that only *scientific testing,* not anecdote or experience, would reveal it. It is consequently not surprising that 71% of the active members of the American Academy of Family Physicians "believe that direct-to-consumer advertising pressures physicians into prescribing drugs that they would not ordinarily prescribe." Rosenthal, Berndt, Donohue, Frank, & Epstein, Promotion of Prescription Drugs to Consumers, 346 New Eng. J. Med. 498-505

(2002) (citing Lipsky, The Opinions and Experiences of Family Physicians Regarding **1513 Direct-To-Consumer Advertising, 45 J. Fam. Pract. 495-499 (1997)).

Of course, the added risks in any such individual case may be small. But those individual risks added together can significantly affect the public health. At least, the FDA and Congress could reasonably reach that conclusion. And that fact, along with the absence of any significant evidence that the advertising restrictions have prevented doctors from learning about, or obtaining, compounded drugs, means that the FDA and Congress could also conclude that the advertising restrictions "directly advance" the statute's safety goal. They help to assure that demand for an untested compounded drug originates with the doctor, responding to an *385 individual's special medical needs; they thereby help to restrict the untested drug's distribution to those most likely to need it; and they thereby advance the statute's safety goals. There is no reason for this Court, as a matter of constitutional law, to reach a different conclusion.

II

I do not believe that Congress could have achieved its safety objectives in significantly less restrictive ways. Consider the several alternatives the Court suggests. First, it says that "the Government could ban the use of 'commercial scale manufacturing or testing equipment for compounding drug products.' " *Ante,* at 1506. This alternative simply restricts compounding to drugs produced in small batches. It would neither limit the total quantity of compounded drugs produced, nor help in any way to assure the kind of individualized doctor-patient need determination that the statute's advertising restriction are designed to help achieve.

Second, the Court says that the Government "could prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received." *Ibid.* This alternative, while addressing the issue of quantity, does virtually nothing to promote the second, need-related statutory objective.

Third, the Court says the Government "could prohibit pharmacists from '[o]ffering compounded drug products at wholesale to other state licensed persons or commercial entities for resale." *Ibid.* This alternative is open to the same objection.

Fourth, the Court says the Government "could limit the amount of compounded drugs, either by volume or by numbers of prescriptions, that a given pharmacist or pharmacy sells out of state." *Ibid.* This alternative, applying only to out-of-state sales, would not significantly restrict sales, either in respect to amounts or in respect to patient need. *386 In fact, it could prevent compounded drugs from reaching out-of-state patients who genuinely need them.

Fifth, the Court says that the Government could "ca[p] the amount of any particular compounded drug, either by drug volume, number of prescriptions, gross revenue, or profit." *Ibid.* This alternative, like the others, ignores the patient-need problem, while simultaneously threatening to prevent compounded drugs from reaching those who genuinely need them, say, a patient whose prescription represents one beyond the arbitrarily imposed quantitative limit.

Sixth, the Court says that the Government could rely upon "non-speech-related provisions of the FDAMA, such as the requirement that compounding only be conducted in response to a prescription." *Ibid.* This alternative also ignores the patient-need problem and was specifically rejected by the Government in the Court of Appeals for the Ninth Circuit. See *supra,* at 1511.

The Court adds that "[t]he Government has not offered any reason why these possibilities, alone or in combination, would be insufficient." *Ante,* at 1506. The Government's failure to do so may reflect the fact that only the Court, not any of the respondents, has here suggested that these "alternatives," **1514 alone or in combination, would prove sufficient. In fact, the FDA's Compliance Policy Guide, from which the Court draws its first four alternatives, specifically warned

that these alternatives alone were insufficient to successfully distinguish traditional compounding from unacceptable manufacturing. See Compliance Policy Guide 77a.

III

The Court responds to the claim that advertising compounded drugs causes people to obtain drugs that do not promote their health, by finding it implausible given the need for a prescription and by suggesting that it is not relevant. The First Amendment, it says, does not permit the Government to control the content of advertising, where ***387** doing so flows from "fear" that "people would make bad decisions if given truthful information about compounded drugs." *Ante,* at 1507. This response, however, does not fully explain the Government's regulatory rationale; it fails to take account of considerations that make the claim more than plausible (if properly stated); and it is inconsistent with this Court's interpretation of the Constitution.

It is an oversimplification to say that the Government "fear[s]" that doctors or patients "would make bad decisions if given truthful information." *Ibid.* Rather, the Government fears the safety consequences of multiple compound-drug prescription decisions initiated not by doctors but by pharmacist-to-patient advertising. Those consequences flow from the adverse cumulative effects of multiple individual decisions each of which may seem perfectly reasonable considered on its own. The Government fears that, taken together, these apparently rational individual decisions will undermine the safety testing system, thereby producing overall a net balance of harm. See, *e.g.,* FDA Reform Legislation 121 (statement of David A. Kessler, Commissioner of the FDA) (voicing concerns about "quality controls" and the integrity of the drug-testing system). Consequently, the Government leaves pharmacists free to explain through advertisements what compounding is, to advertise that they engage in compounding, and to advise patients to discuss the matter with their physicians. And it forbids advertising the specific drug in question, not because it fears the "information" the advertisement provides, but because it fears the systematic effect, insofar as advertisements solicit business, of advertisements that will not fully explain the complicated risks at issue. And this latter fear is more than plausible. See Part I, *supra.*

I do not deny that the statute restricts the circulation of some truthful information. It prevents a pharmacist from including in an advertisement the information that "this pharmacy will compound Drug X." Nonetheless, this Court ***388** has not previously held that commercial advertising restrictions automatically violate the First Amendment. Rather, the Court has applied a more flexible test. It has examined the restriction's proportionality, the relation between restriction and objective, the fit between ends and means. In doing so, the Court has asked whether the regulation of commercial speech "directly advances" a "substantial" governmental objective and whether it is "more extensive than is necessary" to achieve those ends. See *Central Hudson,* 447 U.S., at 566, 100 S.Ct. 2343. It has done so because it has concluded that, from a constitutional perspective, commercial speech does not warrant application of the Court's strictest speech-protective tests. And it has reached this conclusion in part because restrictions on commercial speech do not often repress individual self-expression; they rarely interfere with the functioning of democratic political processes; and they often reflect a democratically determined governmental decision to regulate a commercial venture in order to protect, for example, the consumer, the public health, individual safety, or the environment. See, *e.g., 44 Liquormart, Inc. v. Rhode* ****1515** *Island,* 517 U.S. 484, 499, 116 S.Ct. 1495, 134 L.Ed.2d 711 (1996) ("[T]he State's power to regulate commercial transactions justifies its concomitant power to regulate commercial speech that is 'linked inextricably' to those transactions"); L. Tribe, American Constitutional Law § 12-15, p. 903 (2d ed.1988) ("[C]ommercial speech doctrine" seeks to accommodate "the right to speak and hear expression *about* goods and services" with "the right of government to regulate the sales *of* such goods and services" (emphasis in original)).

I have explained why I believe the statute satisfies this more flexible test. See Parts I and II, *supra.* The Court, in my view, gives insufficient weight to the Government's regulatory rationale, and too readily assumes the existence of practical alternatives. It thereby applies the commercial speech doctrine too strictly. Cf. *Buckman Co. v. Plaintiffs' Legal Comm.,*

531 U.S. 341, 349, 121 S.Ct. 1012, 148 L.Ed.2d 854 (2001) (flexibility necessary ***389** if FDA is to "pursu[e] difficult (and often competing) objectives"). See also *Illinois Bd. of Elections v. Socialist Workers Party,* 440 U.S. 173, 188-189, 99 S.Ct. 983, 59 L.Ed.2d 230 (1979) (Blackmun, J., concurring) (warning against overly demanding search for less restrictive alternatives).

In my view, the Constitution demands a more lenient application, an application that reflects the need for distinctions among contexts, forms of regulation, and forms of speech, and which, in particular, clearly distinguishes between "commercial speech" and other forms of speech demanding stricter constitutional protection. Otherwise, an overly rigid "commercial speech" doctrine will transform what ought to be a legislative or regulatory decision about the best way to protect the health and safety of the American public into a constitutional decision prohibiting the legislature from enacting necessary protections. As history in respect to the Due Process Clause shows, any such transformation would involve a tragic constitutional misunderstanding. See *id.,* at 189, 99 S.Ct. 983 (Blackmun, J., concurring).

IV

Finally, the majority would hold the statute unconstitutional because it prohibits pharmacists from advertising compounded drugs to doctors. *Ante,* at 1508-1509. Doctors, however, obtain information about individual drugs through many other channels. And there is no indication that restrictions on commercial advertising have had any negative effect on the flow of this information. See *e.g.,* Contemporary Pharmacy Practice 11.4 (compounded drug information "available" and "widely disseminated" through books, journals, monographs, and vendors). Nor, with one exception, have doctors or groups of doctors complained that the statute will interfere with that flow of information in the future. But see Brief for Julian M. Whitaker, M.D., et al. as *Amici Curiae* 1 (alleging, without evidentiary support, that the regulations prevent doctors from knowing how to ***390** get "competitively priced compounded drugs as efficiently as possible").

Regardless, we here consider a facial attack on the statute. The respondents here focus their attack almost entirely upon consumer-directed advertising. They have not fully addressed separate questions involving the effect of advertising restrictions on information received by physicians. I would consequently leave these questions in abeyance. Considering the statute only insofar as it applies to advertising directed at consumers, I would hold it constitutional.

For these reasons, I dissent.

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