# IN THE UNITED STATES COURT OF APPEALS
# FOR THE FIFTH CIRCUIT

United States Court of Appeals
Fifth Circuit

**FILED**

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Charles R. Fulbruge III
Clerk

No. 06-51583

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.

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

Before HIGGINBOTHAM, DAVIS, and SMITH, Circuit Judges.

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. According to the American

[1] See Thompson v. W. States Med. Ctr., 535 U.S. 357, 360-61 (2002) (defining compounding); Prof'ls & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 (5th Cir. 1995) (same).

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 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

[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).

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] requiring expensive and

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[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 (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. "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 (continued...)

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]

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[10] (...continued)
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 resi-

(continued...)

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 themSSusing the FDA's traditional lenience toward compounding as an end-run around the new drug approval, adulteration, and misbranding provisions of the FDCA.[14]

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[12] (...continued)

> dues 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; Prof'ls & Patients, 56 F.3d at 593 n.3.

[14] See W. States, 535 U.S. at 362 (summarizing rationale); Professionals & Patients, 56 (continued...)

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]

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[14] (...continued)
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.

(continued...)

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 from the FDCA's new

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[15] (...continued)

> 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.
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> 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.

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, 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

[16] W. States, 535 U.S. at 364 ("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.").

determination." W. States, 535 U.S. at 360.

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]

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[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.

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 ap-

[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).

proval 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 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.

[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.

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.

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.

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 Coun-

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[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).

cil, Inc., 467 U.S. 837 (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, and if so, we "must give effect to the unambiguously expressed intent of Congress," id. at 843. 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).

III.

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 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.

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. 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 (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]

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 definitionSS"not generally recognized . . . as safe and effective"SSinvokes 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

[22] Robinson v. Shell Oil Co., 519 U.S. 337, 340 (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.").

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).

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 drugSSby 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]SSthe composition of the individualized concoction created by a compounding pharmacist will not have been previously approved for use. The resulting substance is therefore a

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[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.

"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), it does not matter that the substance has been created through compounding rather than manufacturingSSwhether 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).

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 § 355(i). Where 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 (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

[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 (continued...)

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." 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.

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 (emphasis added). Pharmacies can therefore avoid Chevron deference only by establishing that congressional intent is in fact not ambiguousSS

[24] (...continued)
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 (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 (2002) (quotation omitted).

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.

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 Association, 531 U.S. 457, 468 (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 provisionsSSit 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 (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.

Most recently, the Court applied the elephant-in-mousehole doctrine in Gonzales v. Oregon, 546 U.S. 243 (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.[26]

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:

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[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, 128 S. Ct. 1183 (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).

> 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]

"Floor statements from two Senators cannot amend the clear and unambiguous language of a statute." Barnhart, 534 U.S. at 457. 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 laws rather than the principal concerns of our legislators by which we are governed." Oncale v. Sundowner Offshore Servs., Inc., 523 U.S.

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[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).

75, 79 (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

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[29] See also Brown & Williamson, 529 U.S. at 147 (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 (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'N 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 ("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.").

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 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 en-

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[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 (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.

forcement 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

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[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 discretionSSbroad 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.

[36] See supra notes 15, 18.

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 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"SStheir 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.

"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. 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

[37] See W. States, 535 U.S. at 366 ("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 ("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 (1988)).

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 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.

In short, Congress's act of amendment gains lawful expression only through enactment of a valid statute.[40] If that act of amendment is invalidSSfor instance, because its unconstitutional portions cannot be severedSSthe 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.

In the supplemental briefing, the FDA argues against severability, and the

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[39] Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc., 447 U.S. 102, 117 (1980) (quoting United States v. Price, 361 U.S. 304, 313 (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 (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 (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 (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").

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.

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 (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 (emphasis added).

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 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.

[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).

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).[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

[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.

> 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).
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> 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 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 (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.

Severing the advertising requirement would leave those other considerable requirements intact, and they would continue to effect Congress's purpose.[43]

[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 (1980), test for regulation of commercial speech:

(continued...)

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.

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).

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[43] (...continued)

> 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.

[44] See, e.g., New York v. United States, 505 U.S. 144, 186-87 (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).

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 premiseSSand as far as we are aware, a premise unsupported by the legislative historySSis 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

[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).

"'strong evidence' that Congress would not have enacted the law without" the advertising provisions. Koog, 79 F.3d at 462 (quoting Alaska Airlines, 480 U.S. at 686). 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. 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 toSSand thereby restrictSSall 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.

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[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).

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 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.

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 (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 itselfSS"shall not apply . . . if"SSand 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.

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.

The district court also considered application of the FDCA to compounded drugs designed for animal use. If it has not been approved, a "new animal drug"

[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).

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.

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,SS
>
> > (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

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[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."

> 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 useSS
>
> > (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
> >
> > (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 useSS

> (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). 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.

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[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.