
VILLANOVA LAW REVIEW

VOLUME 63

2018

NUMBER 3

Articles

REVERSAL OF FORTUNE: MOVING PHARMACEUTICALS FROM OVER-THE-COUNTER TO PRESCRIPTION STATUS?

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“Reality is just a crutch for people who can’t cope with drugs.”

—Robin Williams†

THE opioid “epidemic” recently has grabbed national attention, with regular headlines about the rising number of overdose deaths related to narcotic painkillers, though most occur when patients transition to illicit opiates.¹ Our medicine cabinets hold an equally insidious scourge, however, that gets essentially no attention: nonprescription drugs that cause tens of thousands of deaths annually.² As new risks come to light, the federal government may call for the addition of another line of text on the increasingly crowded labels of these popular products, but consumer behavior suggests that most of us remain blissfully unaware of the potential consequences of our growing dependence on over-the-counter (OTC) drugs, particularly those that previously required visiting a physician.³

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† *Behind the Laughter Was a Harsh Reality; Robin Williams 1951-2014*, *TORONTO STAR*, Aug. 12, 2014, at A1 (calling this “possibly the most famous of his many classic one-liners”).

1. See, e.g., Robert J. Blendon & John M. Benson, *The Public and the Opioid-Abuse Epidemic*, 378 *NEW ENG. J. MED.* 407 (2018); Lawrence O. Gostin et al., *Reframing the Opioid Epidemic as a National Emergency*, 318 *JAMA* 1539 (2017); Joel Achenbach et al., *Opioid Crisis Is a National Emergency, President Says*, *WASH. POST*, Aug. 11, 2017, at A1; Lenny Bernstein & Christopher Ingraham, *Drug Crisis Fuels Drop in At-Birth Life Expectancy*, *WASH. POST*, Dec. 21, 2017, at A20.

2. See Lars Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, 31 *J.L. MED. & ETHICS* 55, 62 (2003) (explaining that nonsteroidal anti-inflammatory drugs (NSAIDs) “may represent a far more serious public health menace [than opioids], contributing to thousands of patient deaths each year”); *infra* Part II.B (elaborating); see also *infra* Part III (discussing the litany of serious hazards associated with other types of popular OTC drug products).

3. See Jane E. Brody, *The Large, Perhaps Outsize, Role of O.T.C.s*, *N.Y. TIMES*, Dec. 1, 2015, at D5.

American consumers spent over \$34 billion on OTC drugs in 2017.⁴ Although that amounts to less than ten percent of annual prescription (Rx) drug sales,⁵ dramatic price differentials between these two categories of products mean that roughly comparable volumes get used.⁶ Demands continue to grow for expanded access to pharmaceuticals without first having to secure a prescription from a physician.⁷ More often than not, the U.S. Food and Drug Administration (FDA) has obliged, allowing a number of drugs to switch to OTC status.⁸ As the agency once explained, non-prescription medications “have an increasingly vital role in the U.S. health care system by providing consumers easy access to certain drugs that can be used safely for conditions that consumers can self-treat without the help of a health care practitioner.”⁹

Although generally greeted with enthusiasm from all concerned, Rx-to-OTC switches do not represent an unalloyed good. In particular, consumers may utilize these increasingly powerful therapeutic agents in far

4. Consumer Healthcare Products Association (CHPA), *OTC Retail Sales 1964–2017*, <https://chpa.org/OTCRetailSales.aspx> [<https://perma.cc/R5UP-PECX>] (last visited Apr. 4, 2018).

5. See Robert Pear, *U.S. to Test Ways to Cut Drug Costs in Medicare*, N.Y. TIMES, Mar. 9, 2016, at A14 (reporting that Americans spent \$457 billion on prescription drugs in 2015).

6. Compare CHPA, *OTC Sales in Volume*, <https://www.chpa.org/OTCSales-Volume.aspx> [<https://perma.cc/G2EX-HVZL>] (last visited Apr. 9, 2018) (showing that almost 5.9 billion units were sold in 2017), with Jeff Donn, *Are We Taking Too Many Drugs?*, NEWSDAY, Apr. 19, 2005, at B13 (reporting that Americans fill 3.5 billion prescriptions annually).

7. See Peter Temin, *Realized Benefits from Switching Drugs*, 35 J.L. & ECON. 351, 352 (1992) (“Concern about the rising cost of medical care has been joined by suspicion of government regulation to create a movement to revive self-medication.”).

8. See, e.g., Serena Gordon, *Sniffing out the Best Allergy Treatment; For Most 12 and Older, Nasal Sprays Are the Way to Go*, CHI. TRIB., Dec. 27, 2017, at D2 (reporting that steroid intranasal sprays such as Flonase[®] and Nasonex[®] have now joined other non-sedating antihistamines switched OTC such as Allegra[®], Claritin[®] and Zyrtec[®]); see also David A. Grimes, *Switching Emergency Contraception to Over-the-Counter Status*, 347 NEW ENG. J. MED. 846, 846 (2002) (“In the past 30 years, over 700 products have been switched from prescription to over-the-counter status. Recent examples include tioconazole, cromolyn sodium, bentoquatam, triclosan, and nicotinic polacrilex.”); FDA, *Prescription to Over-the-Counter (OTC) Switch List*, <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm106378.htm> [<https://perma.cc/CJS2-CPTV>] (last visited Feb. 2, 2018).

9. Public Hearing, *Over-the-Counter Drug Products*, 65 Fed. Reg. 24,704, 24,705 (Apr. 27, 2000); see also *id.* (“Consumers have access to more than 100,000 OTC drug products encompassing more than 800 active ingredients and covering more than 100 therapeutic categories or classes.”); Innovative Approaches for Nonprescription Drug Products; Draft Guidance for Industry, 83 Fed. Reg. 33,938, 33,939 (July 18, 2018) (“FDA believes the innovative approaches described in this draft guidance could lead to the approval of a wider range of nonprescription drug products. FDA currently intends to issue a proposed rule that provides more details regarding the use of additional conditions for [consumer access to OTC products.]”).

too cavalier a fashion.¹⁰ In addition, researchers have discovered a growing number of serious risks associated with some popular OTC drugs even when used appropriately. The FDA, however, seems unwilling to switch these products back to prescription status, preferring instead to handle newly discovered hazards with revisions in labeling. This Article evaluates the reasons for—and the public health consequences of—this reticence to reverse such switches before suggesting that enhanced exposure to tort liability may help prompt sellers to take the initiative.

Part I offers the necessary background about this regulatory arena, first identifying the standards used by the FDA in drawing the prescription/nonprescription line, and then explaining the two basic procedures available for introducing an OTC drug product. Part II focuses on the experience with internal analgesics, in order to briefly illustrate the previously discussed mechanics for making Rx-to-OTC switches before elaborating on the subsequently identified hazards with these products and the agency's generally tepid responses. Part III expands upon this rogues' gallery, identifying other popular nonprescription products that show no sign of returning to prescription status in spite of mounting safety concerns. Part IV asks what accounts for this reluctance to shift dangerous products back and whether either legislative intervention or the threat of tort liability might serve as necessary counterweights. Ultimately, the Article concludes on a fairly pessimistic note about the prospects for confronting this country's underappreciated drug problem.

I. CRITERIA AND METHODS FOR SWITCHING DRUGS TO NONPRESCRIPTION STATUS

The decision over whether a prescription drug can switch to nonprescription status has become increasingly contested.¹¹ When it passed the federal Food, Drug, and Cosmetic Act (FDCA) in 1938,¹² Congress drew

10. See Sandra G. Boodman, *Painful Choices: Consumers Face a Baffling Wall of Choices—and a Surprising Number of Serious Risks—When They Seek Relief from Minor Pains and Illnesses in the Drug Aisle*, WASH. POST, Feb. 11, 2003, at F1; *infra* note 80 and accompanying text.

11. See Eric P. Brass, *Changing the Status of Drugs from Prescription to Over-the-Counter Availability*, 345 NEW ENG. J. MED. 810, 812-15 (2001); Brian L. Strom, *Statins and Over-the-Counter Availability*, 352 NEW ENG. J. MED. 1403, 1403-05 (2005); Gina Kolata, *There's a Blurry Line Between Rx and O.T.C.*, N.Y. TIMES, Dec. 21, 2003, § 4, at 3; Sheryl Gay Stolberg, *F.D.A. Considers Switching Some Prescription Drugs to Over-the-Counter Status*, N.Y. TIMES, June 28, 2000, at A18; see also Lars Noah, *Treat Yourself: Is Self-Medication the Prescription for What Ails American Health Care?*, 19 HARV. J.L. & TECH. 359, 391-92 (2006) ("The choice between prescription and OTC distribution for a pharmaceutical product is nothing to sneeze at. Apart from the potentially enormous financial stakes for all involved—manufacturers, health insurers, and patients/consumers—the classification could have profound public health consequences . . ."); *infra* note 50 (discussing the battle over switching emergency contraception).

12. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-396 (2012)).

no distinction between prescription and OTC pharmaceuticals,¹³ and it apparently had “not intended to restrict in any way the availability of drugs for self-medication.”¹⁴ Nonetheless, when the FDA issued regulations to implement the new legislation later that year, it for the first time provided that certain drugs could not be sold directly to consumers.¹⁵ Six years later, the agency promulgated a rule designating a class of drugs that would be safe only when used “by or under the supervision of a physician.”¹⁶ In one early enforcement case, the FDA successfully prosecuted a seller of testosterone products for making these available as nonprescription drugs.¹⁷

In 1951, the very same year that this case concluded, Congress expressly demarcated prescription drugs as a separate category when it passed the Durham-Humphrey Amendment.¹⁸ New section 503(b)(1) of the FDCA provided in relevant part that a drug, which “because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug, . . . shall be dispensed only” upon a prescription.¹⁹ The statute also

13. It had, however, exempted drugs prescribed by a health professional from certain misbranding prohibitions. *See id.* § 503(b), 52 Stat. 1052 (codified as amended at 21 U.S.C. § 353(b)(2)).

14. H.R. REP. NO. 75-2139, at 8 (1938), *quoted in* United States v. Articles of Drug, 625 F.2d 665, 672 (5th Cir. 1980). “On the contrary, it [wa]s intended to make self-medication safer and more effective.” *Id.*

15. *See* Promulgation of Regulations Under the Federal Food, Drug, and Cosmetic Act, 3 Fed. Reg. 3161, 3168 (Dec. 28, 1938) (appearing as subsection (b)(2) of the rule implementing FDCA § 502(f)); *see also* Peter Temin, *The Origin of Compulsory Drug Prescriptions*, 22 J.L. & ECON. 91, 98-100, 103-05 (1979) (criticizing this development).

16. *See* Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act, 9 Fed. Reg. 12,255, 12,255-56 (Oct. 10, 1944) (codified at 21 C.F.R. § 2.106(b) (1950)); *see also* Peter Barton Hutt, *A Legal Framework for Future Decisions on Transferring Drugs from Prescription to Nonprescription Status*, 37 FOOD DRUG COSM. L.J. 427, 431-32 (1982) (discussing this regulation).

17. *See* United States v. El-O-Pathic Pharmacy, 192 F.2d 62, 74-78 (9th Cir. 1951). Even as approved prescription drugs, testosterone products continue to trouble the FDA. *See* Sabrina Tavernise, *Drugs Using Testosterone Will Label Heart Risks*, N.Y. TIMES, Mar. 4, 2015, at A16 (“[M]anufacturers of testosterone drugs used by millions of Americans will be required to change labels for the drugs to warn that they could increase the risk of heart attacks and strokes and should not be prescribed to treat symptoms in men brought on by age, such as declining sexual drive.”); Steven Woloshin & Lisa M. Schwartz, Opinion, *Sell the Disease to Sell the Drug*, WASH. POST, June 8, 2015, at A15 (“Why are so many men taking testosterone for an unapproved use? The nearly tenfold increase in testosterone prescriptions began in 2007 when Abbott Laboratories (now AbbVie) launched its award-winning ‘Is It Low-T?’ disease awareness campaign.”).

18. *See* Pub. L. No. 82-215, § 1, 65 Stat. 648 (1951) (codified as amended at 21 U.S.C. § 353(b)). Industry representatives opposed an earlier version of this legislation for granting the FDA greater authority to decide which drugs would require a prescription. *See* Temin, *supra* note 15, at 102-03.

19. 21 U.S.C. § 353(b)(1)(A) (2012). A new drug may have to abide by prescription-only availability if so provided in its labeling at the time of approval, but

allowed the FDA to exempt drugs from this requirement if it was “not necessary for the protection of the public health,”²⁰ and a half-century later the agency controversially asserted the power to do so even in the face of objections by the manufacturer of a prescription drug.²¹

When it considers an application for approval of a new drug, the FDA must decide whether to restrict access to it. At least initially, virtually all new ingredients are made available only upon a prescription from—or through direct administration by—a licensed health care professional while the FDA collects additional safety data.²² Premature OTC marketing would further complicate the already difficult process of collecting adverse event reports; instead of relying on information about side effects observed in patients while under the supervision of physicians, the agency would receive sporadic and indiscriminate consumer complaints.²³ Only a

the statute does not separately specify what would prompt such a choice. *See id.* § 353(b)(1)(B); *see also* Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 175–76 (2004) (explaining that the FDA defers to state judgments about who enjoys prescribing privileges); *id.* at 179–80 (same, for controlled substances).

20. 21 U.S.C. § 353(b)(3); *see also* Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-Counter Drug Product, 70 Fed. Reg. 52,050, 52,051 (Sept. 1, 2005) (explaining that one of Congress’ “primary objectives” was “to relieve retail pharmacists and the public from burdensome and unnecessary restrictions on the dispensing of drugs that are safe for use without the supervision of a physician”).

21. *See* Marc Kaufman, *FDA Says It Can Take Away Drugs’ Prescription Status*, WASH. POST, Apr. 26, 2003, at A1 (“FDA officials . . . rested their conclusion, in part, on the FDA’s legal authority to regulate the safety of all drugs, including whether or not they require a doctor’s prescription to ensure the protection of patients.”). I did not buy it:

Although this authority would no doubt justify switching an erstwhile OTC drug to prescription status in light of newly discovered safety concerns, it is difficult to understand how switching from prescription to OTC status would ever promote the safe use of a drug. A switch may serve any number of other valuable ends, and such a move may not present any untoward risk to the public health, but, all other things being equal, is it not inherently (even if only marginally) safer to use a pharmaceutical under the supervision of a health care professional?

Noah, *supra* note 11, at 378; *see also id.* at 383–91 (elaborating on the possible legal objections to such a forced switch).

22. *See* Stephen Paul Mahinka & M. Elizabeth Bierman, *Direct-to-OTC Marketing of Drugs: Possible Approaches*, 50 FOOD & DRUG L.J. 49, 56–57 (1995) (listing the handful of new drugs approved from the outset without prescription restrictions); Temin, *supra* note 7, at 352 (“The burst of technological progress in the drug industry after the Second World War led to the introduction of many new drugs, virtually all of which were marketed as prescription drugs.”).

23. *See* Robin E. Ferner & Keith Beard, *Over the Counter Medicines: Proceed with Caution*, 336 BMJ 694, 696 (2008) (“The safety of over the counter medicines has to be continually reviewed, even though this is difficult in practice. Since health-care professionals may not be involved, we have to rely on patients to report adverse effects.”); Strom, *supra* note 11, at 1403 (“[O]ver-the-counter use renders it more difficult to study a drug’s effects, since prescription databases can no longer be used for that purpose.”).

dozen years ago did Congress obligate all manufacturers of nonprescription products to report adverse events to the FDA.²⁴ A prescription drug later switched OTC will have not only survived the agency's rigorous premarket review process for new chemical entities but also withstood the test of time and a second round of FDA scrutiny.²⁵ Even so, the side effects of some drugs may not come to light until long after initial approval.²⁶

A. *Factors Used in Deciding Suitability for OTC Sale*

Although the statute and regulations provide some general criteria for differentiating between prescription and OTC products, ultimately that determination must be made on an ad hoc basis and without clear guidance.²⁷ The 1951 amendment and the FDA's regulations mention toxicity, other harmful effects, methods of use, and the need for collateral measures,²⁸ but they fail to indicate the point at which one or more of these factors will necessitate prescription-only availability. Toxicity concerns may relate to either acute or chronic effects, and this factor often gets operationalized by reference to a product's "margin of safety" and the extent to which it needs to be carefully titrated for each patient.²⁹ Other

24. See Dietary Supplement and Nonprescription Drug Consumer Protection Act, Pub. L. No. 109-462, § 2(a), 120 Stat. 3469, 3469-72 (2006) (codified at 21 U.S.C. § 379aa (2012)); see also Guidance for Industry on Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application, 74 Fed. Reg. 34,023 (July 14, 2009) (implementing this provision).

25. See Over-the-Counter Human Drugs; Proposed Labeling Requirements, 62 Fed. Reg. 9024, 9027 (Feb. 27, 1997). For instance, in seeking to switch a reduced dosage version of Xenical[®] (orlistat) six years after the FDA's approval of the prescription version, the manufacturer pointed out that 22 million people around the world had taken the drug and that it had been studied in more than one hundred clinical trials enrolling approximately 30,000 subjects. See Sally Squires, *Weighing a Pill for Weight Loss*, WASH. POST, Jan. 24, 2006, at F1.

26. See *infra* Parts II.B & III. In the early 1990s, for example, the FDA received requests to switch the nonsedating antihistamines Seldane[®] (terfenadine) and Hismanal[®] (astemizole) to nonprescription status after several years of prescription marketing, only to see the products withdrawn because of the belated discovery of potentially fatal cardiac side effects. See Bruce Ingersoll, *FDA Proposes to Force Seldane Off the Market*, WALL ST. J., Jan. 14, 1997, at B1; see also Ferner & Beard, *supra* note 24, at 694 ("Safety concerns can emerge with continued use and restraints need to be reimposed. In the UK, the antihistamine terfenadine was reclassified from prescription only to pharmacy status, only to be switched back again when its propensity to cause torsade de pointes [a rare type of arrhythmia] was appreciated.").

27. See Hutt, *supra* note 16, at 428-31. The former chair of the FDA's Nonprescription Drugs Advisory Committee published an article identifying a broad range of issues relevant when considering an Rx-to-OTC switch. See Brass, *supra* note 11, at 811-12 (delineating criteria); *id.* at 812-15 (discussing the broader potential pros and cons of a switch).

28. See 21 U.S.C. § 353(b)(1) (2012); 21 C.F.R. § 330.10(a)(4)(vi) (2018).

29. See Hutt, *supra* note 16, at 433-34; Gerald M. Rachanow, *The Switch of Drugs from Prescription to Over-the-Counter Status*, 39 FOOD DRUG COSM. L.J. 201,

harmful effects may include the risk of interactions with food or other drug products and the potential for abuse.³⁰ Methods of use and “collateral measures” may pose questions about the ability of laypersons to self-diagnose and self-administer as well as the need for periodic clinical monitoring.³¹ No one factor is determinative, however, as a number of approved OTC products raise toxicity, drug interaction, self-diagnosis, and method of administration difficulties.³²

Ultimately, the decision may turn on whether appropriate labeling can help to minimize these problems,³³ notwithstanding the fact that consumers routinely fail to pay attention to product labels.³⁴ FDA regulations

204–05 (1984); see also Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients’ Genetic Profiles*, 43 JURIMETRICS J. 1, 7 & n.25 (2002).

30. The risk of abuse has, from the outset, represented one of the primary rationales for limiting drug products to prescription-only sale. As originally enacted in 1938, the FDCA required a special warning for a list of “habit forming” drugs, but it exempted them so long as prescribed as not refillable. See Pub. L. No. 75–717, §§ 502(d), 503(b), 52 Stat. 1040, 1050, 1052 (1938) (codified as amended at 21 U.S.C. §§ 352(d), 353(b)(2) (1994)), *repealed by* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 126(b), 111 Stat. 2296, 2327. Under a different statute, the Drug Enforcement Administration (DEA) can recommend to the FDA prescription status for an OTC drug with an abuse potential. See 21 U.S.C. § 829(d). Schedule V narcotics with only a limited potential for abuse can remain in OTC status, but a number of states have mandated dispensing of these drugs only by pharmacists and sometimes only with a physician’s prescription. See Gregory M. Fisher, *Third Class of Drugs—A Current View*, 46 FOOD DRUG COSM. L.J. 583, 606–07 (1991) (adding that, before passage of the Controlled Substances Act in 1970, the FDA would handle such concerns by mandating prescription status).

31. The agency sometimes worries that symptomatic relief may mask a serious underlying condition and cause a consumer to delay seeking medical attention. See, e.g., *United States v. Article of Drug . . . Decholin*, 264 F. Supp. 473 (E.D. Mich. 1967) (rebuffing efforts to force an OTC product for gastrointestinal distress into prescription status).

32. See Hutt, *supra* note 16, at 433–40. For example, some OTC drug labels instruct patients to use the product only after having gotten a physician’s diagnosis of a particular condition. See, e.g., Martin S. Lipsky & Theresa Waters, *The “Prescription-to-OTC Switch” Movement: Its Effects on Antifungal Vaginitis Preparations*, 8 ARCHIVES FAM. MED. 297, 298 (1999).

33. See Hutt, *supra* note 16, at 438 (“[P]roblems of toxicity, self-diagnosis, and self-treatment, can either be accentuated by inadequate labeling, or alleviated by adequate labeling. Thus, labeling must be regarded as central to all future determinations of prescription/nonprescription status.”).

34. See *Coffman v. Keene Corp.*, 628 A.2d 710, 717 (N.J. 1993) (adopting the “heeding presumption” for products liability claims in spite of the fact that, “with the proliferation of warnings in our society, it is nearly impossible to go through a day without consciously ignoring warnings designed to protect our health and safety”); Lars Noah, *The Imperative to Warn: Disentangling the “Right to Know” from the “Need to Know” About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 381–84 (1994) [hereinafter Noah, *The Imperative to Warn*]; *id.* at 320 & n.112, 381–82 nn.443–44, 388 (discussing the FDA’s views about this and related concerns in the context of OTC drugs). Indeed, the FDA has lost some of its faith in the ability of labeling to communicate important new risk information to health care professionals and threatened to impose more stringent access restrictions. See Noah, *supra* note 19, at 188 & n.167; see also *id.* at 189–91 (elaborating on possible distri-

provide that nonprescription drug labeling must include directions and warnings “in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.”³⁵ In theory, therefore, the agency would not permit OTC marketing if overly complex labeling were necessary to ensure safe use, and it once took the position that any need to disclose serious risks would defeat a product’s eligibility for nonprescription availability.³⁶ In practice, however, the FDA has required fairly detailed labeling for OTC products as a means of addressing toxicity concerns, serious drug interactions, fears about delaying medical intervention, and so forth.³⁷

In some situations, labeling may attempt to dictate prescription-only use in a subclass of consumers. For instance, most ingested OTC products must include a warning that pregnant or nursing women should “seek the advice of a health professional before using this product.”³⁸ Conversely, when it switched the oxybutynin patch for overactive bladder (Oxytrol[®]) OTC, the FDA did so only for women because physicians first would need

bution restrictions); Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 456 (2002) (“[P]hysicians may tune out if overwhelmed with risk information.”); *cf. id.* at 442 (“[T]he agency’s optimistic assumption [expressed in the course of proposing a rule in 2000] that most physicians rely to some extent on the package insert seems naive.”); Noah, *supra* note 2, at 64 (“[T]he agency may have placed excessive faith in the good sense of physicians and the power of labeling to encourage proper use and to limit the occasions for inappropriate prescribing.”).

35. 21 C.F.R. § 330.10(a)(4)(v) (2018). Almost two decades ago, the agency issued uniform formatting rules designed to improve the readability of OTC drug labels. *See* Over-the-Counter Human Drugs; Labeling Requirements, 64 Fed. Reg. 13,254, 13,286 (Mar. 17, 1999) (codified at 21 C.F.R. § 201.66).

36. *See* Warner-Lambert/Parke-Davis & Co.: Benylin, 44 Fed. Reg. 51,512, 51,525 (Aug. 31, 1979) (“Suitable labeling of an OTC drug may provide sufficient safeguards for a drug that presents such indirect risks [from drowsiness]. When a drug presents serious direct risks (e.g., of cancer or other serious disease), adequate labeling for lay use without medical supervision generally cannot be written.”).

37. *See* Noah, *The Imperative to Warn*, *supra* note 34, at 320–26; *id.* at 320 (“Because few drugs are entirely risk free, OTC drug products can be marketed only if consumers are given information adequate to minimize the danger of any side effects.”); *id.* at 322 (“These ‘Warnings’ are action-oriented directives intended to ensure safe product use rather than mere disclosures of risk information.”); *id.* at 326 (“Because OTC products are intended for self-treatment, the [FDA’s] emphasis on instructional warnings rather than [chronic] risk disclosures seems entirely appropriate.”); *see also infra* Parts II.B & III (discussing the FDA’s tendency to use labeling revisions as a means to deal with newly discovered risk information).

38. Amendment of Labeling Requirements for Over-the-Counter Human Drugs, 47 Fed. Reg. 54,750, 54,757–58 (Dec. 3, 1982) (codified as amended at 21 C.F.R. § 201.63(a)) (applicable to all OTC drugs intended for systemic absorption); *see also id.* at 54,755 (responding to a comment that viewed this proposal as antithetical to OTC status).

to rule out prostate cancer as a possible cause of this condition in men.³⁹ In switching a lower-dose version of the weight-loss drug Xenical[®] (orlistat) to OTC status (sold as Alli[®]), the agency demanded labeling that specified only adult use.⁴⁰ When these sorts of recommendations appear in nonprescription product labeling, however, they do not actually represent prescription restrictions because consumers remain entirely free to disregard such advice.⁴¹

B. *Routes to the Nonprescription Marketplace*

For drugs that do not require the supervision of a physician, have a history of safe use, and present no abuse potential, the FDA has a pair of ways to authorize OTC marketing.⁴² First, a company may sell a nonprescription drug if it abides by the terms of the applicable “monograph,” which specifies for a particular category of products the active ingredients and dosages that the agency has determined to be “generally recognized” as safe and effective (GRAS/E), along with the precise labeling necessary to facilitate appropriate consumer use.⁴³ Any continued prescription mar-

39. See FDA, *Need Relief from Overactive Bladder Symptoms?*, <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm426099.htm> [<https://perma.cc/U5ZC-UTMG>] (last visited Feb. 2, 2018).

40. See Diedtra Henderson, *1st Over-Counter Diet Pill Approved; Use Requires Other Weight-Loss Steps*, BOS. GLOBE, Feb. 8, 2007, at A1 (“[T]he FDA approved Alli for sale only to those who are at least 18 years old. The agency, however, stopped short of restricting access to the drug through such measures as requiring that it be placed behind a pharmacist’s counter or requiring proof of age at purchase.”); cf. Julie P. Karpinski et al., *Smoking Cessation Treatment for Adolescents*, 15 J. PEDIATRIC PHARMACOLOGY & THERAPEUTICS 249, 258 (2010) (“[W]hile the OTC purchase of [nicotine replacement therapy] is not permitted by adolescents, adolescents may obtain the products under the supervision of a physician via a prescription.”).

41. See *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 173 (E.D.N.Y. 2013) (observing that “a diet drug, Alli, ‘was approved [OTC] for weight loss in 2007 only for adults 18 and older,’ although it could be purchased by teenagers”); *id.* at 180 (noting “[t]he FDA’s willingness to rely on labeling to make these drugs available for sale over-the-counter without any age or point-of-sale restrictions, even though they are unsafe for unsupervised use by young adolescents”); *id.* at 184 (same).

42. See *Parke-Davis & Co. v. Califano*, 564 F.2d 1200, 1201–03 (6th Cir. 1977); Stan Stringer, *What Has Been Happening with Over-the-Counter Drug Regulation*, 53 FOOD & DRUG L.J. 633, 635 (1998). Anyone may initiate an effort to exempt a product from prescription status. See 21 C.F.R. § 310.200(b) (2018). Although an interested party presumably could try to use comparable procedures for going in the opposite direction, no parallel rule so specifies.

43. See 21 C.F.R. § 330.1 (2018); see also *Cutler v. Hayes*, 818 F.2d 879, 883–85 (D.C. Cir. 1987) (describing the OTC drug review process); Kenneth C. Baumgartner, *A Historical Examination of the FDA’s Review of the Safety and Effectiveness of Over-the-Counter Drugs*, 43 FOOD DRUG COSM. L.J. 463 (1988) (offering an exhaustive review of the first decade and a half). After the agency issues a final monograph, marketing of an OTC product outside of its scope would require favorable FDA action on either a petition to amend the monograph or an application for new drug approval. See Robert G. Pinco & Michael W. Cogan, *Prescription to Over-the-Counter Switches: An Example of the Need for New Procedures in the Post-Monograph Era*, 39 FOOD DRUG COSM. L.J. 230, 235–38 (1984).

keting of active ingredients for indications recognized in an OTC monograph would constitute a misbranding violation under the FDCA.⁴⁴ Conversely, nonmonograph ingredients, dosages, and indications could only be marketed under an approved new drug application (NDA).⁴⁵ The FDA has used the monograph process as a mechanism for switching dozens of drugs formerly limited to prescription-only use.⁴⁶

The second route to OTC marketing requires that a company file a supplement to an approved NDA or a separate NDA for a reformulation (including revised labeling and perhaps reduced dosage) of a product

44. See 21 C.F.R. § 310.200(d); see also 21 U.S.C. § 353(b)(4)(B) (2012) (providing that a drug exempted from prescription requirements would be misbranded if it used the prescription warning statement or otherwise suggested that it is for prescription use); Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Combination Drug Products, 53 Fed. Reg. 30,522, 30,527 (Aug. 12, 1988) (to be codified at 21 C.F.R. pt. 341) (“[A]fter the effective date of the final OTC drug monograph (usually 12 months after its publication in the *Federal Register*), if the ingredient and indication are included in the monograph, a drug product containing the ingredient as switched to OTC status may not be marketed as a prescription product.”).

45. See *NRDC v. FDA*, 710 F.3d 71, 75 (2d Cir. 2013) (“Like a recipe, each monograph sets out the FDA-approved active ingredients for a given therapeutic class of OTC drugs and provides the conditions under which each active ingredient is GRAS/E. . . . Manufacturers desiring to market OTC drugs that are excluded from the monograph may not do so without obtaining individualized FDA approval.”). If an active ingredient got excluded for failing to satisfy the criteria for allowing OTC sale (and, hence, would “misbrand” an OTC product containing such an ingredient), then the NDA would have to propose use of prescription labeling. If, instead, an ingredient got excluded from a monograph based on a judgment that it lacked general recognition of safety or effectiveness, then a sponsor willing to undertake clinical trials to produce such evidence could file an NDA seeking approval as an OTC drug. See *Rachanow*, *supra* note 29, at 208 (explaining that this had happened with the sleep-aid doxylamine succinate); see also *United States v. Articles of Drug . . . Promise Toothpaste*, 826 F.2d 564, 569-73 (7th Cir. 1987) (holding that the manufacturer of a combination product for dental sensitivity should have done so because it fell outside of the terms of the pending OTC monograph).

46. See *Fisher*, *supra* note 30, at 612; *id.* at 627 (“[T]he OTC Drug Review greatly accelerated the prescription-to-nonprescription switch movement, reflecting the conclusions of experts that at least forty theretofore prescription ingredients are safe and effective for use by consumers on a nonprescription basis.”); see also *Marketing Status of Ingredients Recommended for Over-the-Counter Use*, 41 Fed. Reg. 32,580, 32,581-82 (Aug. 4, 1976) (codified at 21 C.F.R. § 330.13) (inviting use of the OTC drug review to switch prescription products). Occasionally, the FDA has accomplished what amounts to an OTC switch from a different baseline—namely, prohibiting sale of a product as a dietary supplement or food but allowing sale as a nonprescription drug. See *Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk*, 69 Fed. Reg. 6788, 6793 (Feb. 11, 2004) (codified at 21 C.F.R. pt. 119); *Proposed Rule, Saccharin and Its Salts*, 42 Fed. Reg. 19,996, 20,004 (Apr. 15, 1977) (to be codified in scattered parts of 21 C.F.R.); *cf. Nat’l Nutritional Foods Ass’n v. Mathews*, 557 F.2d 325, 334-36 (2d Cir. 1977) (invalidating rules that treated high-dose vitamin A and D products as prescription drugs).

previously approved for prescription use.⁴⁷ Manufacturers generally initiate switches of drugs that remain subject to NDAs, though they sometimes fail to persuade the FDA to take this action.⁴⁸ The agency may require that the applicant conduct so-called actual use and label comprehension studies.⁴⁹ Dual marketing of an active ingredient for both a prescription and OTC use is possible under limited circumstances.⁵⁰ For instance, the agency has approved ibuprofen (e.g., Motrin[®]) at different dosages as a prescription and an OTC analgesic.⁵¹ In the event of reduced dosage for-

47. See 21 C.F.R. § 330.11; *id.* § 310.201(a) (listing these previously approved active ingredients); Public Hearing, Over-the-Counter Drug Products, 65 Fed. Reg. 24,704, 24,704–05 (Apr. 27, 2000). In some cases, after several years of OTC marketing under the terms of an NDA, the FDA may propose including an ingredient in the relevant monograph, which would allow other companies to sell it without having to secure a separate license to do so. See, e.g., Sunscreen Drug Products for Over-the-Counter Human Use, Amendment to the Tentative Final Monograph, 61 Fed. Reg. 48,645 (Sept. 16, 1996) (to be codified at 21 C.F.R. pt. 352).

48. See, e.g., *United States v. An Undetermined Quantity . . . Benylin Cough Syrup*, 583 F.2d 942, 944–46 (7th Cir. 1978); Andrew Pollack, *Pfizer Is Said to Want New Lipitor Drug*, N.Y. TIMES, Aug. 4, 2011, at B4 (“Merck failed three times to win the agency’s approval for over-the-counter versions of Mevacor . . . Bristol-Myers Squibb also failed to obtain approval for an over-the-counter version of Pravachol, another [cholesterol-lowering] statin.”).

49. See, e.g., *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 171–79, 189–91 (E.D.N.Y. 2013) (discussing at length the label comprehension and actual use studies submitted in support of switching emergency contraceptive products); see also Brass, *supra* note 11, at 811–12, 814; R. William Soller, *The Over-the-Counter Scientific/Regulatory Paradigm*, 33 DRUG INFO. J. 799, 801–02 (1999).

50. See Drug Approvals: Circumstances Under Which an Active Ingredient May Be Simultaneously Marketed in Both a Prescription Drug Product and an Over-the-Counter Drug Product, 70 Fed. Reg. 52,050, 52,051 (Sept. 1, 2005) (offering a half dozen examples where “some meaningful difference exists” between two approved versions of products containing the same active ingredient). After initially refusing to switch an emergency contraceptive (the so-called “morning after pill”), the FDA viewed dual marketing as a compromise, wanting to require a prescription below a certain age, which it kept shifting, even though the drug had an unimpeachable safety profile. Its foot-dragging attracted tremendous controversy, and it took a court order to force the agency’s hand and allow full OTC availability. See *Tummino*, 936 F. Supp. 2d at 166, 197–98, *denial of stay pending appeal*, 936 F. Supp. 2d 198, 209 (E.D.N.Y. 2013); *id.* at 200 (“The effort to convert these levonorgestrel-based contraceptives from prescription to over-the-counter status has gone on for over twelve years, even though they would be among the safest drugs available to children and adults on any drugstore shelf.”); see also Michael D. Shear & Pam Belluck, *Obama to Drop Limit on Selling a Contraceptive*, N.Y. TIMES, June 11, 2013, at A1 (reporting that the government decided against appealing the decision). See generally Lisa Heinzerling, *The FDA’s Plan B Fiasco: Lessons for Administrative Law*, 102 GEO. L.J. 927 (2014).

51. See Linda M. Katz, *Prescription to Over-the-Counter Drug Switches*, 48 FOOD & DRUG L.J. 567, 567 (1993) (differentiating such dual status products from “a complete switch”); see also Stephanie Saul, *F.D.A. Approves an Over-the-Counter Version of the Weight-Loss Drug Xenical*, N.Y. TIMES, Feb. 8, 2007, at A16. Even less frequently, the FDA has permitted continued prescription marketing of a drug for some uses (e.g., gastrointestinal reflux disease) while it switched the same strength product OTC when labeled for other uses (e.g., heartburn). See Alex Berenson, *Where Has All the Prilosec Gone?*, N.Y. TIMES, Mar. 2, 2005, at C1.

mulations, it did not take long for consumers to realize that they could self-medicate with a prescription strength simply by exceeding the dose recommended in the labeling.⁵²

By all accounts, the OTC monograph process has gotten bogged down. Decades have passed with some major categories still unfinished.⁵³ In 2014, for instance, frustrated that it took the FDA more than thirty years to finalize most of the monograph for products intended to protect against sun exposure, Congress unanimously passed legislation designed to expedite the continuing review as well as to facilitate the approval of novel ingredients.⁵⁴ Conversely, and in contrast to the greater ease of calling for revisions in the labeling of products switched through the NDA mechanism, the agency has expressed frustration about its inability to respond to new data because it would have to initiate rulemaking to amend a monograph.⁵⁵ Congress may soon take action on this broader front,⁵⁶

52. See Brass, *supra* note 11, at 812, 814; Emilie le Beau, *A Dose of Caution: Whether You're Big or Small, Don't Self-Correct Drug Amounts*, CHI. TRIB., Dec. 18, 2005, at Q9 (“Forty-eight percent of people admitted to taking more than the recommended dose of an OTC drug, believing it would make the drug more effective, according to a recent survey by the National Council on Patient Information and Education.”); see also *Bober v. Glaxo Wellcome PLC*, 246 F.3d 934, 939–40, 942 (7th Cir. 2001) (rejecting a state law consumer fraud claim against the manufacturer of Zantac® (ranitidine) for suggesting that two doses of the 75 mg OTC version could not be substituted for the prescribed 150 mg version); Lance W. Rook, *Listening to Zantac: The Role of Non-Prescription Drugs in Health Care Reform and the Federal Tax System*, 62 TENN. L. REV. 107, 119 n.65 (1994) (“The drug manufacturer’s ability to claim that its OTC product used to be available only by prescription appears to be a big marketing advantage. This is, presumably, because drugs that were once available only by prescription are viewed as more potent than non-switched OTC medications.”).

53. See Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 447–48 & n.71 (2008); see also *NRDC v. FDA*, 710 F.3d 71, 75–76, 80–83 (2d Cir. 2013) (allowing a public interest group, which alleged that triclosan used in antibacterial soaps may act as an endocrine disruptor and endanger health, to challenge the agency’s delay in finalizing the OTC monograph for topical antiseptics after it had proposed 35 years earlier to exclude this ingredient).

54. See Sunscreen Innovation Act, Pub. L. No. 113–195, § 2, 128 Stat. 2035, 2035–45 (2014) (codified at 21 U.S.C. §§ 360fff to 360fff-5); Brady Dennis, *The Biggest Impasse Under the Sun*, DENV. POST, May 18, 2015, at 1C. This legislation included provisions designed to speed the review of non-sunscreen ingredients as well. See Proposed Rule, *FDA Review and Action on Over-the-Counter Time and Extent Applications*, 81 Fed. Reg. 19,069, 19,072, 19,084–86 (Apr. 4, 2016) (to be codified at 21 C.F.R. §§ 330.14–.15).

55. See Public Hearing, *Over-the-Counter Drug Monograph System—Past, Present, and Future*, 79 Fed. Reg. 10,168, 10,170 (Feb. 24, 2014); see also *id.* (conceding that many monographs have not yet gotten finalized, and, for these and other reasons, seeking public comments about the continued viability of this mechanism).

56. See Elyse Stoltz Dickerson, Opinion, *Over-the-Counter Medicines Deserve Better Treatment*, FT. WORTH STAR-TELEGRAM (Tex.), Sept. 27, 2017; Malcolm Spicer, *OTC Monograph Reform Momentum Carries Potential Exclusivity Snag*, ROSE SHEET, Jan. 18, 2018, available in Lexis News library.

making it a good time to highlight a different set of questions that no one seems to be terribly interested in confronting—namely, when and how should the FDA revisit the fundamental judgment about a product’s suitability for OTC marketing?

II. NONNARCOTIC PAINKILLERS OFFER A CAUTIONARY TALE

Because analgesics relieve symptoms and do not purport to treat any underlying disease process, they would seem to represent natural candidates for OTC marketing.⁵⁷ Nonetheless, even if most consumers would not need a physician’s diagnostic skills in order to decide whether to select a particular pain reliever, and putting to one side narcotic analgesics that raise concerns about abuse and diversion, the safety profile of such products may justify restrictions on access. Thus, the FDA requires prescription labeling when it first approves a new analgesic product, and many of these drugs never get switched OTC.⁵⁸ After they do manage to leave prescription status, however, no amount of evidence of newly discovered hazards seems enough to warrant switching them back; instead, time and again, the agency prefers to add still more information to the labels of these drugs.

A. *Transitioning Analgesics to Unsupervised Availability*

The OTC drug review for internal analgesics commenced with a call for data in 1972.⁵⁹ Five years later, the advisory panel, which had considered forty-nine active ingredients, issued its recommendations.⁶⁰ More

57. See Noah, *supra* note 2, at 57. On the flimsiness, however, of the distinction between symptoms and disease, see Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241, 262-63 (1999).

58. See Noah, *supra* note 2, at 56-58. After all, COX-2 inhibitors (e.g., Vioxx®) looked like potential switch candidates because they claimed to avoid a side effect associated with OTC analgesics (and were costing insurers a mint), see Dennis Cauchon, “Complex Issues” Require Much Study Before Action, *FDA Says: Administration’s Decision on Allergy Drugs Could Have Wide Repercussions*, USA TODAY, Apr. 12, 2000, at 5A, but the belated discovery of cardiac risks put an end to any such possibility, see Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES, Nov. 14, 2004, § 1, at 1. Newer research suggests, however, that the sole remaining COX-2 inhibitor poses no greater cardiovascular hazards than analgesic products available OTC. See Gina Kolata, *Celebrex Is Found to Be No Riskier for Hearts Than Other Pain Drugs*, N.Y. TIMES, Nov. 14, 2016, at A20.

59. See *Over-the-Counter Internal Analgesic and Antirheumatic Drug Products, Safety and Efficacy Review, Request for Data and Information*, 37 Fed. Reg. 14,633 (July 21, 1972). The review included the use of such products for reducing inflammation and fever as well as for relieving pain.

60. See *Establishment of a Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products*, 42 Fed. Reg. 35,346, 35,350, 35,422-34 (July 8, 1977) (to be codified at 21 C.F.R. pt. 343) (concluding, for instance, that a few ingredients used in then-marketed analgesics (e.g., phenacetin) were not GRAS/E); see also Baumgartner, *supra* note 43, at 484 (“Two leading OTC pain reliever products, in advance of the publication of the TFM, removed ingredients, including the ingredient phenacetin, not shown to be GRAS/E.”).

than a decade later, the FDA published a tentative final monograph (TFM) for this OTC drug category.⁶¹ In brief, this proposed rule included aspirin and acetaminophen as permitted active ingredients and allowed labeling “[f]or the temporary relief of minor aches and pains” with directions against taking analgesic products for more than ten days, accompanied by an assortment of warning statements.⁶² In addition, during the pendency of this OTC drug review, the FDA promulgated a requirement that any nonprescription products containing aspirin include a special warning against use during pregnancy.⁶³ More than forty years after the advisory panel completed its work, however, the monograph for internal analgesics remains unfinished.⁶⁴

Apart from this still-pending monograph process, some sponsors of analgesics approved for prescription-only sale filed supplemental NDAs requesting OTC status. In 1960, a dozen years before starting on the monograph, the FDA authorized nonprescription marketing of lower doses of acetaminophen (e.g., Tylenol®).⁶⁵ A quarter of a century later, the agency approved OTC sale of a lower dose product containing ibuprofen, a non-steroidal anti-inflammatory drug (NSAID).⁶⁶ Thereafter it switched several other NSAIDs, including naproxen (e.g., Aleve®) and ketoprofen

61. See Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use, Tentative Final Monograph, 53 Fed. Reg. 46,204 (Nov. 16, 1988) (to be codified at 21 C.F.R. pts. 310, 343, 369).

62. See *id.* at 46,255–56. The TFM includes a number of warnings applicable to aspirin. See *id.* at 46,256 (to be codified at 21 C.F.R. § 343.50(c)).

63. See Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Products; Final Rule, 55 Fed. Reg. 27,776, 27,784 (July 5, 1990) (codified at 21 C.F.R. § 201.63(e)); see also Martha M. Werler et al., *Use of Over-the-Counter Medications During Pregnancy*, 193 AM. J. OBSTETRICS & GYNECOLOGY 771, 776 (2005) (finding that use of aspirin by pregnant women has decreased while their use of other OTC drugs has increased); *id.* at 777 (“The common use of OTC medicines in pregnancy necessitates further studies to establish safety or to identify risks.”).

64. The latest unified regulatory agenda shows this and several other monographs under the “long-term actions” heading. See Regulatory Agenda, 83 Fed. Reg. 1860, 1861, 1864–65 (Jan. 12, 2018).

65. See Natasha Singer, *Robert L. McNeil Jr., 94; Introduced Tylenol Brand*, N.Y. TIMES, June 4, 2010, at A25 (“Approved by the [FDA], Tylenol went on the market as a prescription medication in 1955. It became an over-the-counter drug in 1960.”). The agency actually had exempted acetaminophen from prescription dispensing requirements a few years earlier. See Republication of Regulations, 20 Fed. Reg. 9525, 9648 (Dec. 20, 1955) (codified as renumbered at 21 C.F.R. § 310.201(a)(1)).

66. See Irvin Molotsky, *Agency Approves Painkiller for Over-the-Counter Sales*, N.Y. TIMES, May 19, 1984, § 1, at 1; see also *supra* note 51 and accompanying text (explaining that higher doses remained in prescription status). Many years later, the FDA proposed amending the TFM to add ibuprofen as a monograph ingredient. See Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph, and Related Labeling, 67 Fed. Reg. 54,139, 54,158–59 (Aug. 21, 2002) (to be codified at 21 C.F.R. pts. 201, 343).

(e.g., Orudis[®]), to nonprescription status.⁶⁷ Consumers today can select among a wide array of painkillers.

B. *Accumulating and Communicating New Risk Information*

OTC analgesics may pose significant risks,⁶⁸ which the agency generally has tried to handle through revisions in labeling. In addition to concerns about kidney and liver damage, researchers have linked prolonged use of NSAIDs to sometimes fatal gastrointestinal bleeding.⁶⁹ Then, in the early 1980s, the FDA became aware of a suspected link between Reye's syndrome and the use of aspirin by children suffering from viral infections.⁷⁰ The labels of OTC drug products containing aspirin and related ingredients now must include the following statement: "Children and teenagers who have or are recovering from chicken pox or flu-like symptoms should not use this product. When using this product, if changes in behavior with nausea and vomiting occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness."⁷¹ Notably, when it originally mandated an earlier version of this warning, the agency had rejected suggestions urging "more drastic measures [such as] banning use of aspirin in products for individuals under 21 years of age or limiting such products to prescription use."⁷²

67. See Gary Mays, *Pain-Killer Wars Can Be a Pain for Ailing Consumers; Product Proliferation Likely Will Continue as Firms Try to Provide Greater Flexibility*, CHI. TRIB., Nov. 24, 1995, at B1.

68. See Boodman, *supra* note 10, at F1 ("Each year, . . . about 16,000 die from complications related to the use of OTC painkillers. . . . Some health officials say that the actual number of injuries and deaths is considerably higher because many cases go unrecognized or unreported, especially among the elderly, many of whom take multiple medications."); Mary Duenwald, *Choosing a Pain Remedy Carefully*, N.Y. TIMES, July 6, 2004, at F5.

69. See Noah, *supra* note 2, at 65 nn.19–20, 67 n.52; Jane E. Brody, *Finding Better Ways to Manage Pain*, N.Y. TIMES, Sept. 5, 2017, at D5 ("In addition to cardiovascular risks, NSAIDs can cause gastrointestinal problems, damaging the lining of the digestive tract, especially when they are not taken with food. Their most serious side effects include ulcers, bleeding, kidney failure and, in rare cases, liver failure.")

70. See Proposed Labeling for Oral Aspirin-Containing Drug Products, 50 Fed. Reg. 51,400, 51,401 (Dec. 17, 1985); see also Pub. Citizen Health Research Group v. Comm'r, FDA, 740 F.2d 21, 34–35 (D.C. Cir. 1984) (remanding for lower court to consider a claim of unreasonable delay by the FDA in acting on a citizen petition urging it to require a warning of this risk); Am. Home Prods. Corp. v. Johnson & Johnson, 672 F. Supp. 135, 137–41 (S.D.N.Y. 1987) (offering a detailed account of the history behind the early Reye's syndrome warning efforts).

71. 21 C.F.R. § 201.314(h)(1) (2018).

72. Labeling for Oral and Rectal Over-the-Counter Aspirin and Aspirin-Containing Drug Products; Reye Syndrome Warning, 53 Fed. Reg. 21,633, 21,635 (June 9, 1988); see also United States v. Article of Drug . . . "Decholin," 264 F. Supp. 473, 482 n.9 (E.D. Mich. 1967) (noting that the FDA would not limit aspirin to prescription use even though "at the root of a headache may lie anything from nervous tension to a malignant brain tumor"); cf. Harvey J. Weiss, *Aspirin: A Dangerous Drug?*, 229 JAMA 1221 (1974) (suggesting prescription-only status). In contrast, with mounting reports of emergency room visits for young children using

More recently, after it received reports of an association between acetaminophen and liver toxicity, the FDA imposed special warning requirements.⁷³ Even in the absence of alcohol consumption, reports of liver toxicity from accidental overdoses have increased with the expanding use of acetaminophen in combination prescription as well as nonprescription drug products.⁷⁴ Hence, acetaminophen exhibits a narrow margin of safety,⁷⁵ which typically makes an ingredient ineligible for OTC availability.⁷⁶

In addition, the FDA has called for warnings that acetaminophen may cause the sometimes fatal skin conditions Stevens-Johnson Syndrome and toxic epidermal necrolysis,⁷⁷ which NSAIDs already had to disclose.⁷⁸ The

OTC cough-cold remedies, the industry opted to add an age limitation (four-year-olds and older) in product labeling. See Gardiner Harris, *Cold Drugs for Children Will Carry New Warning*, N.Y. TIMES, Oct. 8, 2008, at A17 (adding that the companies previously had stopped marketing these products for use in children under two-years of age); see also Matthew Perrone, *FDA Warns Teething Medicines Unsafe, Wants Them off Shelves*, ST. LOUIS POST-DISPATCH, May 24, 2018, at A1 (“[V]arious gels and creams containing the drug benzocaine can cause rare but deadly side effects in children, especially those 2 years and younger. The agency has been warning about the products for a decade but said reports of illnesses and deaths have continued . . . [and] there is little evidence they actually work.”). As explained earlier, however, such age restrictions—in this case directed to parents and guardians—function only as advisories. See *supra* notes 40–41 and accompanying text.

73. See *Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning*, 63 Fed. Reg. 56,789, 56,801–02 (Oct. 23, 1998) (codified at 21 C.F.R. § 201.322) (warning against the use of internal analgesics in combination with heavy alcohol consumption); see also *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378, 1387, 1389 (4th Cir. 1995) (sustaining a negligence claim and punitive damage award against the seller of Tylenol where it had delayed submitting adverse reaction reports—concerning liver toxicity resulting from interactions between acetaminophen and alcohol—to the FDA during the OTC drug review for internal analgesics).

74. See Deborah Franklin, *Poisonings from a Popular Pain Reliever Are on the Rise*, N.Y. TIMES, Nov. 29, 2005, at F5; Matthew Perrone, *Tylenol, Implicated in Liver Failure, Will Carry New Warning*, BOS. GLOBE, Aug. 30, 2013, at B7 (“Overdoses from acetaminophen send 55,000 to 80,000 people to the emergency room in the United States each year and kill at least 500, according [to] the Centers for Disease Control and Prevention and the [FDA].”); see also Melissa Dribben, *Suits Against Tylenol Maker Seek to Highlight Dangers*, PHILA. INQUIRER, Feb. 16, 2014, at G1 (discussing criticism of the FDA’s slow and limited responses to this problem).

75. See Dribben, *supra* note 74, at G1 (“[I]t has a narrow margin of safety and can quickly become toxic when taken in doses not much greater than the recommended limits, or when combined with alcohol.”); Denise Gellene, *Even at Advised Doses, Tylenol May Harm Liver; Though Overdoses Have Been Linked to Organ Damage, the Study Is the First to Suggest Trouble in Healthy People Taking the Drug as Directed*, L.A. TIMES, July 5, 2006, at A13.

76. See *supra* note 29 and accompanying text.

77. See *Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions; Guidance for Industry*, 82 Fed. Reg. 3332, 3333 (Jan. 11, 2017).

78. See *FDA Links Painkiller to Fatal Skin Conditions*, WASH. POST, Aug. 2, 2013, at A10 (“Other drugs used to treat fever and pain, such as ibuprofen and

agency also has ordered stronger warnings about the increased risk of heart attack and stroke associated with aspirin and NSAIDs such as ibuprofen.⁷⁹ Notwithstanding the growing litany of risk disclosures for OTC analgesics, many consumers regularly exceed the recommended doses or otherwise disregard information appearing in the labeling for these drugs.⁸⁰

III. ESCALATING CONCERNS ABOUT THE HAZARDS POSED BY OTHER OTC DRUGS

The track record with internal analgesics hardly represents an outlier. This Part catalogs newly discovered dangers associated with popular non-prescription treatments for heartburn and allergies as well as hazards linked to unexpected patterns of abuse with a pair of other products. As it did in the case of OTC pain relief products, the FDA typically responded with calls for revised labeling. Only once in recent memory has the agency proposed rescinding nonprescription status for an ingredient that it previously (though only tentatively) had authorized for unsupervised use.

Because NSAIDs irritate the lining of the stomach, consumers often take heartburn remedies to guard against this side effect, but doing so (or taking them for other reasons) may bring a new set of problems.⁸¹ Proton pump inhibitors, an effective new class of drugs for treating gastric distress,⁸² again illustrate what can happen after an Rx-to-OTC switch. In

naproxen, also carry the risk of serious skin conditions, but the risk is already described in the warning section of those drug labels, the FDA said.”).

79. See Sabrina Tavernise, *F.D.A. Is Set to Toughen Nonaspirin Warnings*, N.Y. TIMES, July 10, 2015, at A20; see also Gary C. Curhan et al., *Frequency of Analgesic Use and Risk of Hypertension in Younger Women*, 162 ARCHIVES INTERNAL MED. 2204, 2207–08 (2002) (finding that the use of NSAIDs and acetaminophen caused an increase in blood pressure but that aspirin did not); Scott Hensley, *Rethinking Over-the-Counter Drugs: Finding on Aleve Underscores Dearth of Overall Research; Little Incentive for Trials*, WALL ST. J., Dec. 22, 2004, at D1 (reporting that naproxen “appeared to increase by about 50% the risk of cardiovascular problems, such as strokes and heart attack, in elderly patients taking the drug daily for several years”). Indeed, the finding on naproxen prompted the FDA to impose its toughest risk labeling revision (i.e., a “black box” warning) for prescription versions, but it allowed continued marketing of OTC versions with nothing more than the addition of a simple warning statement. See Marc Kaufman, *Another Pain Reliever Pulled; FDA Warns of Risk in Entire Class of Anti-Inflammatories*, WASH. POST, Apr. 8, 2005, at A1.

80. See Jane E. Brody, *Perils of Pain Relief Often Hide in Tiny Type*, N.Y. TIMES, May 3, 2005, at F7 (“[F]ar too many people use [analgesics] carelessly, without adequate attention to dosage and warnings about possible risks.”); Alan Mozes, *Opioids Aren’t America’s Only Painkiller Problem*, CHI. TRIB., Feb. 7, 2018, at D6 (“Among those surveyed who take over-the-counter ibuprofen (Motrin, Advil), 15 percent admitted to exceeding daily maximum dosage”); see also *supra* note 52 (discussing consumers’ tendency to exceed the recommended individual doses of OTC drugs).

81. See Joe Graedon & Teresa Graedon, *Dangers of OTC Drugs Often Given Short Shrift*, BALT. SUN, Jan. 5, 2017, at C4.

82. Histamine H₂ receptor antagonists (a.k.a. H₂ blockers) represented an earlier generation of heartburn drugs and witnessed several major Rx-to-OTC

2003, after initially rejecting an application, the FDA allowed Prilosec[®] (omeprazole) to leave prescription status for certain uses.⁸³ Some critics expressed concerns about this decision, pointing out that unsupervised use might mask more serious underlying conditions that then would go undiagnosed and untreated, but the agency viewed that possibility as remote.⁸⁴ Other proton pump inhibitors soon followed Prilosec into the nonprescription marketplace, including Prevacid[®] (lansoprazole) and Nexium[®] (esomeprazole).⁸⁵

Before long, however, worrisome reports about these OTC drugs began to accumulate.⁸⁶ First, researchers discovered that users became more prone to a dangerous and difficult-to-treat type of intestinal infection.⁸⁷ Second, proton pump inhibitors appeared to interact with certain anticoagulants that rendered these critical prescription drugs less effective.⁸⁸ Third, researchers found that long-term use of proton pump inhib-

switches (sold under brand-names such as Pepcid[®], Tagamet[®] and Zantac[®]). See Davina C. Ling et al., *Deregulating Direct-to-Consumer Marketing of Prescription Drugs: Effects on Prescription and Over-the-Counter Product Sales*, 45 J.L. & ECON. 691, 693–96, 703, 705–06 (2002). The FDA handled drug interaction concerns through disclosures in their labeling. See Francesca Lunzer Kritz, *The Prescription-to-Nonprescription Switch; Drug Agency Weighs Change of Status for Several Medicines*, WASH. POST, July 25, 1995, at Z7 (“[T]he asthma drug theophylline; warfarin, a blood thinner; or phenytoin, a drug to treat epilepsy . . . leave the body much more slowly when mixed with Tagamet and can result in extremely rare instances in a buildup that could cause convulsions and coma.”).

83. See Gardiner Harris, *F.D.A. Approves Over-Counter Sales of Top Ulcer Drug*, N.Y. TIMES, June 21, 2003, at A1 (reporting that earlier efforts to switch Prilosec had faltered).

84. See Hope Cristol, *Heartburn of Another Kind: For Some Patients, Self-Treating with New OTC Drugs May Invite Trouble*, WASH. POST, Sept. 30, 2003, at F1 (“While Prilosec labeling warns heartburn sufferers to see a doctor if symptoms persist after 14 days, it does not address the risk of cancer or Barrett’s esophagus.”); see also Shari Roan, *When Antacids Aren’t Enough; That Chronic Heartburn Could Be a Sign of Something More Serious; Doctors Are Seeing More Cases of Rare but Deadly Esophageal Cancer*, L.A. TIMES, Apr. 10, 2006, at F1.

85. See Nicholas Bakalar, *Drug: Heartburn Drugs and Mortality*, N.Y. TIMES, July 11, 2017, at D4. The OTC drug Zegrid[®] combines the active ingredient in Prilosec with sodium bicarbonate. At present, other proton pump inhibitors, including AcipHex[®] (rabeprazole), Dexilant[®] (dexlansoprazole), and Protonix[®] (pantoprazole), remain Rx-only.

86. See Adam J. Schoenfeld & Deborah Grady, Editorial, *Adverse Effects Associated with Proton Pump Inhibitors*, 176 JAMA INTERNAL MED. 172, 172–74 (2016) (summarizing newly discovered hazards); Dennis Thompson, *Heartburn Meds May Increase Risk of Death; Study Warns of Prolonged Use of Drugs*, CHI. TRIB., July 19, 2017, at D6.

87. See Sandra Dial et al., *Use of Gastric Acid-Suppressive Agents and the Risk of Community-Acquired Clostridium difficile-Associated Disease*, 294 JAMA 2989, 2992 (2005) (focusing on prescription versions of these drugs); Seema Yasmin, *Heartburn Meds May Trigger Gut Infection*, SAN DIEGO UNION TRIB., May 9, 2017, at E1.

88. See Alicia Mundy, *FDA Underscores Plavix Warning*, WALL ST. J., Oct. 20, 2010, at D2 (“Federal regulators said they plan to reiterate a warning that patients taking the anticlotting drug Plavix should avoid also taking the heartburn drug Prilosec . . .”); *id.* (explaining that a black box warning was added to the labeling for this prescription anticoagulant to highlight the suspected interaction).

itors was associated with seizures,⁸⁹ fractures,⁹⁰ dementia,⁹¹ heart attacks,⁹² stroke,⁹³ liver disease,⁹⁴ and kidney problems.⁹⁵ Putting aside uncertainties about a causal connection or the frequency of such effects, though the agency took many of these seriously enough to communicate new risk information,⁹⁶ it seems entirely implausible to think that the FDA would have authorized Rx-to-OTC switches in light of such concerns.⁹⁷ Nonetheless, because these questions came to light only after the fact, the agency so far has shown no indications that it might force previously switched proton pump inhibitors back into prescription-only status.

Older antihistamines such as diphenhydramine (sold under brand-names such as Benadryl®) have long included warnings that they may cause sedation. Indeed, some have become more popular as sleep aids

89. See Kay Lazar, *Acid Reflux in Flux; The FDA Warns That Long-Term Use of Proton Pump Inhibitors Could Have Adverse Effects, So Doctors Are Reevaluating the Popular Medication*, BOS. GLOBE, Apr. 4, 2011, at G12 (reporting that the agency warned that regular users “may end up with low magnesium levels, which can put them at risk for seizures, irregular heartbeats, and muscle spasms”).

90. See *id.* (“Last May, the FDA said the drugs, both sold as prescriptions and over-the-counter, may increase the risk of hip, wrist, and spine fractures, especially for patients who are over 50 and have been taking them for longer than one year or are receiving high doses.”).

91. See Nicholas Bakalar, *Behavior: P.P.I.s Tied to Dementia*, N.Y. TIMES, Feb. 23, 2016, at D6; see also Catherine Saint Louis, *Study Links Long-Term Use of Acid-Suppressing Drugs to Vitamin B12 Deficiency*, N.Y. TIMES, Dec. 11, 2013, at A17.

92. See Lenny Bernstein, *Heartburn Drugs Linked to Higher Heart Attack Risk*, WASH. POST, June 11, 2015, at A1.

93. See Dennis Thompson, *Do Common Heartburn Drugs up Risk of Stroke?*, CHI. TRIB., Dec. 7, 2016, at D4.

94. See Bradley J. Fikes, *Stomach Acid Blockers Promote Liver Disease*, SAN DIEGO UNION TRIB., Oct. 11, 2017, at A1.

95. See Lenny Bernstein, *Popular Heartburn Pills Linked to Kidney Disease*, WASH. POST, Jan. 12, 2016, at A3.

96. See Lazar, *supra* note 89, at G12; Paula Span, *Heartburn Solutions, and Problems*, N.Y. TIMES, Feb. 2, 2016, at D5 (“The [FDA] has also issued several safety announcements about these drugs’ association with C. diff, fracture risk and low magnesium, linked to kidney disease and other ailments.”).

97. Cf. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Combination Drug Products Containing Promethazine Hydrochloride Marketing Status, 54 Fed. Reg. 36,762, 36,764 (Sept. 5, 1989) (deferring to an advisory committee recommendation against the agency’s proposal to allow OTC marketing of the antihistamine promethazine hydrochloride until it could resolve safety questions such as the risk of sudden infant death syndrome); Rob Stein, *Nonprescription Sales of Cholesterol Drug Rejected: FDA Panel Says Risk of Side Effects Outweighs Benefits*, WASH. POST, Jan. 15, 2005, at A3 (“[T]he advisers were concerned that pregnant women might take the drug [Mevacor®], resulting in birth defects, and that patients might suffer rare but potentially life-threatening liver and muscle complications. . . . FDA officials said the company’s own research showed that consumers frequently misunderstood who should take the drug”); *F.D.A. Reviews Nonprescription Claritin*, N.Y. TIMES, Apr. 30, 2002, at C12 (reporting that, before switching loratadine, the FDA looked into reports of a cluster of birth defects in Sweden that arose one decade after original approval). In other words, if the FDA knew back then what we know now about these products, then it would never have permitted OTC status.

(sold under brand-names such as Unisom[®]) for this very reason. Nonetheless, concerns about daytime sleepiness in users of these OTC antihistamines continue as have urgent calls for enhanced warnings.⁹⁸ In the early 1990s, after studies had linked another sedating antihistamine (doxylamine succinate) to the development of liver and thyroid tumors in rodents, the FDA flirted with the idea of requiring a disclosure of this information in product labeling.⁹⁹ More recently, researchers have uncovered an association between dementia and long-term use of the broader class of anticholinergics, which includes diphenhydramine and doxylamine among other OTC as well as prescription ingredients.¹⁰⁰ Of course, these and other hazards would not present a problem if consumers conscientiously followed instructions on product labels calling only for short-term use.¹⁰¹

Similarly, a potential for abuse, which normally would count against an active ingredient's eligibility for nonprescription access,¹⁰² may not become evident until long after approval. Such concerns prompted the FDA to consider removing ipecac syrup from OTC status. In 1965, it had authorized marketing of this product, which induces vomiting, so long as sold in small containers and labeled for use only as directed by a physician, hospital, or poison control center.¹⁰³ After reports of abuse by persons with eating disorders such as bulimia (as well as by parents with Munchausen syndrome), coupled with reasons to doubt that it actually helped in cases of poisoning, the agency decided to revisit its decision: in 2003, it put

98. See Dennis Cauchon, *Why Allergy Drugs Cost So Much*, USA TODAY, Apr. 12, 2000, at 1A ("estimat[ing] that sedating antihistamines cause an average of about 600 auto fatalities per year"); Jeff Zeleny, *NTSB Says Drugs Need More Label Warnings; Drowsiness Cited as Contributing to Many Crashes*, CHI. TRIB., Nov. 15, 2001, at A24.

99. See Noah, *The Imperative to Warn*, *supra* note 34, at 324–26 (discussing this proposal, and explaining that the agency dropped the idea in 1994).

100. See Lisa Rapaport, *Some Common Drugs May Cause Brain Changes*, WASH. POST, Apr. 26, 2016, at E3; see also Shelly L. Gray et al., *Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study*, 175 JAMA INTERNAL MED. 401, 405–06 (2015) (focusing on prescription drugs from this broad class, though noting that several first-generation antihistamines are available as OTC medications); cf. Kathryn Richardson et al., *Anticholinergic Drugs and Risk of Dementia: Case-Control Study*, 361 BMJ k1315 (2018) (exonerating antihistamines in this class though implicating the incontinence drug oxybutynin).

101. Cf. *Torsiello v. Whitehall Labs.*, 398 A.2d 132, 137–40 (N.J. App. Div. 1979) (holding that a jury could find the direction on Anacin[®] (aspirin and caffeine) to consult a physician if pain lasted for more than ten days was inadequate to guard against the risk of gastrointestinal bleeding from prolonged use); *Michael v. Warner/Chilcott*, 579 P.2d 183, 186–87 (N.M. Ct. App. 1978) (same, for an instruction on a decongestant containing phenacetin not to take the drug for more than ten days without consulting a physician because it may cause kidney damage, even though this language tracked a regulation that the FDA had promulgated in 1964).

102. See *supra* note 30 and accompanying text.

103. See *Ipecac Syrup in One Fluid Ounce Containers; Required Warnings and Directions*, 30 Fed. Reg. 13,628 (Oct. 27, 1965) (codified as renumbered at 21 C.F.R. § 201.308).

the question before one of its advisory committees,¹⁰⁴ which voted to recommend against continued nonprescription availability.¹⁰⁵ Perhaps recognizing that no seller then would have sought approval of a prescription-only substitute,¹⁰⁶ however, the agency failed to act on the advice that it had received.¹⁰⁷

In 2016, evidence emerged that the antidiarrheal agent loperamide (sold under brand-names such as Imodium[®]) had unexpectedly become a drug of abuse and caused serious injuries.¹⁰⁸ The FDA responded first by demanding that labels warn against ingesting such high doses, and then it asked manufacturers to adopt more cumbersome blister packs for each dose and include only enough doses for short-term use.¹⁰⁹ Although evidently not on the table as an option, the agency could switch loperamide back to prescription-only use without much difficulty because, like a few other OTC products,¹¹⁰ the ingredient remains separately approved as a prescription drug at a higher dose; the FDA could simply withdraw its approval of the OTC version, which would leave legitimate consumers still able to secure access through their physicians.

In rare cases, newly discovered risks with an OTC drug prompt more drastic action than simply a call for additional information in labeling. For example, the agency belatedly withdrew its *tentative* approval of phenylpropanolamine (PPA), a nasal decongestant used in OTC cough-

104. See Nonprescription Drugs Advisory Committee; Notice of Meeting, 68 Fed. Reg. 24,004 (May 6, 2003). Consumers with anorexia or bulimia also frequently abuse OTC laxative products in ways that may endanger their health wholly apart from the underlying eating disorder. See James L. Roerig et al., *Laxative Abuse: Epidemiology, Diagnosis and Management*, 70 DRUGS 1487, 1499 (2010).

105. See Elena Conis, *Home Poison Aid Falls out of Favor; Ineffectiveness and Abuse Lead the FDA to Reevaluate Ipecac*, L.A. TIMES, July 28, 2003, at F5 (“The FDA’s non-prescription drug advisory committee voted 6 to 4 last month in favor of revoking ipecac’s over-the-counter status. An FDA official said the agency was considering a range of options for the syrup, . . . [including] a labeling change that would warn users against taking ipecac for weight loss.”); see also Michael Shannon, *The Demise of Ipecac*, 112 PEDIATRICS 1180, 1181 (2003).

106. See Jennifer Huget, *Time to Purge the Ipecac?*, WASH. POST, July 8, 2003, at F1 (“It may take months or longer for the FDA to decide whether to strip ipecac of its OTC status. That change wouldn’t mean that ipecac would simply move to prescription-only status; individual manufacturers would have to submit their products for FDA review . . . [, and] ipecac might not meet the FDA’s standards for prescription drugs’ safety and efficacy.”).

107. After years of regularly forecasting that it would issue a notice of proposed rulemaking (NPRM) within a matter of months, see, e.g., Unified Agenda, 70 Fed. Reg. 64,568, 64,575 (Oct. 31, 2005) (anticipating issuance of an NPRM by June 2006), the FDA announced that it had dropped the idea, see Unified Agenda, 77 Fed. Reg. 7946, 7955 (Feb. 13, 2012) (indicating that it had “withdrawn” action item no. 357 on Sept. 8, 2011).

108. See Catherine Saint Louis, *Addicts Who Can’t Find Painkillers Turn to Anti-Diarrhea Drugs*, N.Y. TIMES, May 11, 2016, at A10.

109. See Laurie McGinley, *FDA Looks to Curb Abuse of Anti-Diarrhea Drug Used as Methadone Substitute*, WASH. POST, Jan. 31, 2018, at A3.

110. See *supra* notes 50–52 and accompanying text (discussing dual status products).

cold and weight-loss products (sold under brand-names such as Dimetapp[®] and Dexatrim[®]), after scientists confirmed a long-suspected association with hemorrhagic stroke.¹¹¹ After first proposing the addition of a warning statement on nonprescription drugs while awaiting the results of this study,¹¹² the FDA issued a public health advisory in 2000 and a proposed rule to withdraw PPA from the market altogether in 2005.¹¹³ The time that it took for the agency to take these steps,¹¹⁴ and the evidence that it demanded before accepting the link between this nonessential ingredient and a grave though rare side effect, demonstrate once again just how reticent the FDA has become about revisiting a decision to allow nonprescription availability.¹¹⁵

111. See Jeff Gerth & Sheryl Gay Stolberg, *Another Part of the Battle: Keeping a Drug on the Shelves of Stores*, N.Y. TIMES, Dec. 13, 2000, at A31 (reporting that the FDA estimated 200–500 strokes annually); see also Walter N. Kernan et al., *Phenylpropranolamine and the Risk of Hemorrhagic Stroke*, 343 NEW ENG. J. MED. 1826, 1830–32 (2000); Glaser v. Thompson Med. Co., 32 F.3d 969 (6th Cir. 1994) (finding sufficient evidence that the PPA in Dexatrim could have caused the plaintiff's stroke); *In re Phenylpropranolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d 1230 (W.D. Wash. 2003), *further proceedings*, 227 F.R.D. 553, 567–69 (W.D. Wash. 2004) (approving \$60 million class action settlement); Barbara J. Rothstein et al., *A Model Mass Tort: The PPA Experience*, 54 DRAKE L. REV. 621, 635 (2006) (“The court [hearing the multidistrict litigation] also found, however, that the scientific research did not support expert testimony concerning the causal link between PPA and other injuries [alleged by plaintiffs], including seizures, psychoses, cardiac injuries, and any [stroke] injury occurring more than seventy-two hours after ingestion.”).

112. See *Over-the-Counter Drug Products Containing Phenylpropranolamine; Required Labeling*, 61 Fed. Reg. 5912, 5915 (Feb. 14, 1996) (to be codified at 21 C.F.R. § 201.321), *withdrawn*, 73 Fed. Reg. 75,625 (Dec. 12, 2008) (explaining that its subsequent proposal to withdraw PPA superseded this proposed warning requirement).

113. See *Phenylpropranolamine-Containing Drug Products for Over-the-Counter Human Use; Tentative Final Monographs*, 70 Fed. Reg. 75,988, 75,997 (Dec. 22, 2005) (to be codified at 21 C.F.R. § 310.545); *id.* at 75,994 (“In November 2000, FDA issued a public health advisory . . . [N]ational chain drugstore[s] and major and smaller manufacturers voluntarily removed phenylpropranolamine-containing OTC drug products from the market.”). For another recent public health advisory issued by the FDA, this one to alert consumers of OTC antiseptic products of a small possibility of severe anaphylactic reactions, see FDA, *Chlorhexidine Gluconate: Drug Safety Communication—Rare but Serious Allergic Reactions* (Feb. 2, 2017), <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm590808.htm> [<https://perma.cc/4RY3-A35A>] (last visited Feb. 2, 2018).

114. See Sarah Lueck, *FDA Officials Suspected PPA Link to Higher Stroke Risk Since '80s*, WALL ST. J., Nov. 8, 2000, at B6. Although the agency's announcement prompted remedial action by most manufacturers, the FDA still has not formally ordered the withdrawal of this active ingredient; the latest unified regulatory agenda shows final action on this proposal remains “To Be Determined” with regard to PPA's use in weight-loss products. See *Regulatory Agenda*, 83 Fed. Reg. 1860, 1865 (Jan. 12, 2018); *cf.* *Regulatory Agenda*, 76 Fed. Reg. 40,052, 40,066 (July 7, 2011) (indicating that it had withdrawn the proposal with regard to PPA's use in cough-cold products).

115. In two other instances, the FDA proposed an Rx-to-OTC switch but backpedaled far more quickly in the face of strong objections voiced by health professionals. See Noah, *supra* note 11, at 372–74 (discussing the bronchodilator

During the OTC drug review process that had commenced in 1972, the agency did remove several products from nonprescription status,¹¹⁶ but these involved ingredients that it had never before scrutinized.¹¹⁷ When the FDA excluded certain active ingredients from its monographs, this happened because of an insufficient showing of effectiveness or perhaps unresolved questions about safety when used without medical supervision. In either case, sponsors would remain free to secure agency approval of a nonprescription drug containing such ingredients so long as they could produce adequate evidence of safety and effectiveness.¹¹⁸ In

metaproterenol (Alupent®) and exocrine pancreatic insufficiency products). If such objections had arisen only after the finalization of these monographs, however, the agency may not have bothered acting upon any such change of heart.

116. See Baumgartner, *supra* note 43, at 491 (“Final rules have also been issued banning or removing from the market, principally for safety reasons, camphorated oil, daytime sedatives, hexachlorophene, insect repellents (internal), overindulgence (inebriation) remedies, salicylanilides, sweet spirits of nitre, and zirconium (aerosol).” (footnotes omitted)); *id.* at 480 (“In another significant safety measure not accomplished formally under the OTC drug review, the FDA in 1979 issued approximately 350 letters to drug manufacturers requesting that they recall antihistamine drug products containing methapyrilene after it was determined that the ingredient was a potential carcinogen.”); Fisher, *supra* note 30, at 606 (“In the 1960s the FDA addressed several questions of toxicity, abuse, and misuse of certain nonprescription drugs, including amyl nitrite inhalants, amphetamine and methamphetamine inhalers, and others, by placing them on prescription.”); *id.* at 607 (adding that, during the OTC drug review, the agency “remov[ed] from the market several nonnarcotic nonprescription drug ingredients and several classes of nonprescription drug products” (footnote omitted)); *id.* at 627 (referencing “FDA activities designed to restrict the use of certain nonprescription drug ingredients or certain classes of nonprescription drug products, such as placing them on prescription”).

117. *Cf.* Am. Pub. Health Ass’n v. Veneman, 349 F. Supp. 1311, 1317 (D.D.C. 1972) (expressing concern about the FDA’s decision, once it established the monograph process, against publishing 260 reports solicited from the National Academy of Sciences-National Research Council (NAS-NRC) rating nonprescription drugs in light of the fact that one “report on over-the-counter drugs indicates that only 25% of such drugs are effective”); *id.* at 1317 n.19 (“The FDA has just released for publication an NAS-NRC report on over-the-counter drugs, specifically cold remedies, that was submitted to the FDA three years ago. The report indicates that many of the nation’s leading cold medications lack substantial evidence of effectiveness and are subject to withdrawal.”). In a set of regulations that largely predated the OTC drug review, the FDA demanded prescription status for more than a dozen ingredients. See Reorganization and Republication, 40 Fed. Reg. 13,996, 14,034–37 (Mar. 27, 1975) (codified as amended at 21 C.F.R. §§ 250.12–108).

118. See *supra* note 45. Something like this happened, for instance, with a popular acne ingredient after questions about its safety arose. In 1985, the FDA tentatively concluded that low concentrations of benzoyl peroxide qualified as GRAS/E, but six years later it deferred final action on this ingredient until it could resolve new concerns about possible carcinogenicity. See Topical Acne Drug Products for Over-the-Counter Human Use; Final Monograph, 56 Fed. Reg. 41,008, 41,008–09 (Aug. 16, 1991) (noting that animal studies suggested this ingredient may promote tumors). Although it allowed continued OTC marketing while it awaited the results of promised new studies, the FDA proposed warnings about avoiding sun exposure, see Topical Drug Products Containing Benzoyl Peroxide; Required Labeling, 60 Fed. Reg. 9554, 9557 (Feb. 17, 1995) (to be codified at 21

contrast to the FDA's evident willingness to jettison questionable nonprescription ingredients that it has not previously green-lighted, this Article focuses on drugs that have gotten the agency's blessing for OTC use and asks why such basic judgments about appropriate categorization seem to become largely unalterable.

IV. TRYING TO PUT THE GENIE BACK IN THE (PRESCRIPTION) BOTTLE

When it initiated the OTC drug review in the early 1970s, the FDA plainly envisioned that switches might go in either direction.¹¹⁹ It also viewed such judgments as not “frozen in time.”¹²⁰ In 2000, when it announced a public hearing about its policies regarding Rx-to-OTC switches, the agency asked tangentially whether “older therapies that may provide less benefit or more risk [should] be removed from the OTC market.”¹²¹ Almost two decades later, it has not offered an answer, though the FDA's longstanding pattern of behavior suggests a lack of interest in unswitching any drugs that it has moved to nonprescription status.¹²²

C.F.R. § 201.318(b)), and in the preamble it suggested possibly sharing information about tumor risks with consumers through leaflets inserted in product packages, *see id.* at 9555–56 (helpfully supplying text to use); *see also id.* at 9556–57 (strongly encouraging manufacturers to voluntarily relabel their products even before finalization of the rule). In the end, after the submission of reassuring studies, the FDA added the ingredient to the OTC monograph and decided against requiring any disclosures about its earlier safety concerns. *See* Final Rule, Classification of Benzoyl Peroxide as Safe and Effective and Revision of Labeling to Drug Facts Format; Topical Acne Drug Products for Over-the-Counter Human Use, 75 Fed. Reg. 9767, 9776 (Mar. 4, 2010) (codified at 21 C.F.R. pt. 333).

119. *See* Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. 9464, 9470 (May 11, 1972) (¶ 70); Hutt, *supra* note 16, at 429–30 (quoting the FDA Chief Counsel as explaining at the outset of the process that it would be about “confirming the OTC status [of every drug under review], perhaps changing some from prescription to OTC or perhaps going the other way and changing some from OTC to prescription”); *id.* at 430 (same, in instructing review panels: “[T]he opposite is also true. If there are over-the-counter drugs today that you think should be switched to prescription, then we want you to give us that advice also.”); *cf.* Fisher, *supra* note 30, at 611 (“As the [OTC Drug] Review progressed, it became clear that advisory review panels would recommend switching an appreciable number of ingredients from prescription to nonprescription status, but not vice versa.”).

120. *See* Hutt, *supra* note 16, at 431 (“Consideration of the proper status of drugs is inherently transitory.”); *see also id.* at 433 (“Congress recognized [in 1951] that the determination of prescription/nonprescription status would never be static, but must continually evolve on the basis of new information.”).

121. Public Hearing, Over-the-Counter Drug Products, 65 Fed. Reg. 24,704, 24,705 (Apr. 27, 2000).

122. Arguably, the agency's review of substances used in food reflects a similar tendency. *See* Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U. L. REV. 329, 382–85 (1998) (explaining that, when new safety concerns arise about substances previously identified as “generally recognized as safe” (GRAS), the FDA moves them into an “interim” food additive category where they may remain indefinitely); *see also* Monica Eng, *Who Tests the Safety of New Ingredients in Food?: Too Often, U.S. Lets Manufacturers Make the Call on Their Own Products, Critics Say*, CHI. TRIB., Aug. 26, 2012, at A1 (“[A] few substances

No doubt this reluctance to revisit judgments about suitability for OTC marketing reflects skewed incentives faced by most of the interested parties.¹²³ Although legislative action occasionally forces the issue, it might take broader reforms of the stark distinction between prescription and nonprescription status to overcome the striking disinclination to revisit an Rx-to-OTC switch. Alternatively, the prospect of tort liability might incentivize sellers to restrict consumer access, though the defense of implied federal preemption as presently configured would stand in the way of efforts by plaintiffs to employ negligent marketing theories of recovery.

A. *Lack of Incentives to Use Available Regulatory Mechanisms*

First, the FDA might not relish the procedural obstacles presented by trying to unravel an Rx-to-OTC switch. The Durham-Humphrey Amendment had called for doing so “by regulation,”¹²⁴ which represents a route that this agency increasingly prefers to avoid whenever possible.¹²⁵ As demonstrated by the serious delays that it has encountered in finalizing the OTC monographs, rulemaking hardly offers an expeditious mechanism for responding to serious new risk information. Indeed, the FDA recently has preferred issuing technically non-binding guidance documents to call for revisions in the labeling of nonprescription products.¹²⁶

Although switching the status of products governed by OTC monographs seemingly would necessitate amending the rules, prescription drugs switched through the NDA process instead could get switched back by amending the revised license. Although the sponsor of such a

initially considered GRAS have later been found to pose health risks and were subsequently banned by the FDA. The most recent of these decisions was in 1986, when the FDA prohibited the use of sulfites as a preservative on raw produce due to severe allergic reactions in those sensitive to sulfites.”).

123. Cf. Joshua P. Cohen et al., *Switching Prescription Drugs to Over the Counter*, 330 *BRIT. MED. J.* 39, 39 (2005) (“Switches are motivated mainly by three factors: pharmaceutical firms’ desire to extend the viability of brand names; attempts by healthcare funders to contain costs; and the self care movement. Making drugs available over the counter affects a large number of stakeholders”); Dennis Cauchon, *Better Drugs May Be Stuck Behind Counter: Makers Prefer Slow Route to OTC Market*, *USA TODAY*, June 27, 2000, at 9D; Elyse Tanouye & Thomas M. Burton, *More Firms “Switch” Prescription Drugs to Give Them Over-the-Counter Status*, *WALL ST. J.*, July 29, 1993, at B1.

124. See 21 U.S.C. § 353(b)(3) (2012). *But cf.* *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 197–98 (E.D.N.Y. 2013) (suggesting that it might not necessitate rulemaking, though focusing only on an Rx-to-OTC switch and of a product with an approved NDA rather than subject to an existing OTC monograph).

125. See Lars Noah, *Governance by the Backdoor: Administrative Law(lessness?) at the FDA*, 93 *NEB. L. REV.* 89, 94-97 (2014).

126. See, e.g., Recommended Warning for Over-the-Counter Acetaminophen-Containing Drug Products and Labeling Statements Regarding Serious Skin Reactions; Guidance for Industry, 82 Fed. Reg. 3332 (Jan. 11, 2017); Over-the-Counter Pediatric Oral Liquid Drug Products Containing Acetaminophen; Guidance for Industry, 80 Fed. Reg. 46,588 (Aug. 5, 2015); see also Noah, *supra* note 125, at 103, 113–22 (detailing the FDA’s shift toward guidance-making).

nonprescription drug might resist and exercise its right to demand a hearing,¹²⁷ the FDA has various ways of short-circuiting this adjudicatory process.¹²⁸ In either case, however, a lack of resources may pose the biggest obstacle. Chronic underfunding exists for the OTC division, at least relative to those units that review new prescription drugs because only they get user fee proceeds.¹²⁹ An Rx-to-OTC switch accomplished through a supplemental NDA would require payment by the sponsor of at least \$1.2 million,¹³⁰ but apparently no one other than Congress would foot the bill for unswitching.

Manufacturers would have no particular incentives to move a product back into prescription status. In contrast, as patents and non-patent regulatory exclusivities expire on a prescription drug, which means that competitors introducing lower-cost generics threaten to take most of the brand-name company's market share, a switch to OTC status provides manufacturers with various means of extending their revenue streams.¹³¹ First, an OTC switch may entitle the sponsor to additional protection against generic competition: if the FDA required the sponsor to conduct additional studies in order to support approval, then the successful appli-

127. See Noah, *supra* note 11, at 385, 387.

128. See Noah, *supra* note 125, at 123 (“Congress has delegated to the agency increasingly elaborate licensing powers, but these also came with demanding procedures. The FDA has, however, deployed these various tools in creative ways” (footnote omitted)); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 911–12, 914 n.73 (2008).

129. See Kate Sheridan, *These Companies Are Eager to Pay FDA Fees; Goal Is Fast Reviews of OTC Products*, BOS. GLOBE, Aug. 25, 2017, at B9.

130. See Prescription Drug User Fee Rates for Fiscal Year 2018, 82 Fed. Reg. 43,244, 43,247 tbl.7 (Sept. 14, 2017) (noting that this fee represents half the charge for applications that require the submission of clinical data). If the license holder initiated the process of unswitching, then they would file another NDA supplement and again pay this user fee.

131. See Cohen et al., *supra* note 123, at 40 (discussing loratadine and omeprazole); Holly M. Spencer, Comment, *The Rx-to-OTC Switch of Claritin, Allegra, and Zyrtec: An Unprecedented FDA Response to Petitioners and the Protection of Public Health*, 51 AM. U. L. REV. 999, 1023–24, 1038–41 (2002); Milt Freudenheim, *Rearranging Drugstore Shelves: More Products Shift to Nonprescription*, N.Y. TIMES, Sept. 27, 1994, at D1; Gabriella Stern & Rose Gutfeld, *Vote Sets Back P&G, Syntex on Analgesic*, WALL ST. J., June 3, 1993, at B1 (“Most big pharmaceutical companies are trying to switch to the over-the-counter category as a source of new revenue at a time when prescription drug revenues are under pressure.”). Other reasons that sellers might favor an Rx-to-OTC switch have, however, faded with time. See Noah, *supra* note 11, at 380 n.110 (“[N]ow that manufacturers enjoy the freedom to advertise prescription pharmaceuticals directly to consumers (coupled with the spread of insurance coverage for prescription drugs), many of the older incentives to secure OTC status appear to have vanished.”). Recent developments in products liability doctrine have created disincentives to switching. See *id.* at 378–83; *id.* at 364 (“[A]n Rx-to-OTC switch might increase a seller’s exposure to liability”); see also *infra* Part IV.C (elaborating). Nonetheless, when it opts to pursue a switch, the sponsor must believe that enough of an upside remains to counterbalance the possibility of enhanced tort exposure.

cant would receive an additional three-year period of market exclusivity.¹³² Second, with or without this extended protection, an OTC switch means that generics could compete only in the nonprescription marketplace, clearing the way for the brand-name sponsor to introduce a purportedly new and improved product in the prescription marketplace without fear of getting undercut by generic versions of their original drug.¹³³ Neither one of these tactical maneuvers, however, operates in the other direction, so brand-name companies would see little to gain from moving their product back to prescription status—generic competitors would automatically tag along in that case.¹³⁴

In addition, switching affects regulatory jurisdiction over the advertising of these products: the FDA has the authority to supervise promotional campaigns for prescription drugs,¹³⁵ while the Federal Trade Commission (FTC) supervises nonprescription drug advertising.¹³⁶ For the most part, the Commission's standards offer somewhat greater flexibility than those

132. See *Apotex, Inc. v. Shalala*, 53 F. Supp. 2d 454, 458 & n.4 (D.D.C. 1999); Berenson, *supra* note 51, at C1 (reporting that Prilosec had received this additional period of marketing exclusivity); see also *Upjohn Co. v. Kessler*, 938 F. Supp. 439, 443–45 (W.D. Mich. 1996) (declining to issue a preliminary injunction where the manufacturer of Rogaine® (minoxidil) failed to establish a likelihood of success on the merits of its claim that the FDA should have granted its request for market exclusivity after an Rx-to-OTC switch). Moreover, once any exclusivity period expires for a product switched OTC, state laws requiring generic substitution only apply to pharmacists dispensing prescription drugs, which means that brand loyalty by consumers will allow the sponsor to retain greater market share even when competing against lower-priced products offered by competitors.

133. See, e.g., Francesca Kritz, *A Side Effect Felt in the Wallet: With Generic Prilosec Due, the \$6 Billion Drug's Maker Offers a High-Priced Successor*, WASH. POST, Mar. 13, 2001, at T6; Rita Rubin, *Claritin Going OTC: Will Heir Be a Prescription for Success?*, USA TODAY, Apr. 23, 2002, at 11D; see also Lars Noah, *Product Hopping 2.0: Getting the FDA to Yank Your Original License Beats Stacking Patents*, 19 MARQ. INTELL. PROP. L. REV. 161, 168–69 (2015). If, however, the FDA initially rejects a switch petition and generic competitors enter the prescription market, then the brand-name company may not bother trying again even if subsequently produced evidence would amply support a transition to OTC status. See Noah, *supra* note 11, at 363–64 n.26 (explaining that rejection of an OTC switch petition “creates a ‘prescription orphan,’” and concluding that “the alignment of the various parties’ interests after the entry of generic prescription substitutes results in a suboptimal outcome”).

134. Insulin does not represent an exception. Long available as an OTC drug notwithstanding difficulties with self-diagnosis and administration, see Hutt, *supra* note 16, at 436–37, newer versions that enjoyed patent protection require a prescription, see *Fast-Acting Insulin Approved*, N.Y. TIMES, June 18, 1996, at C7; see also Jeremy A. Greene & Kevin R. Riggs, *Why Is There No Generic Insulin? Historical Origins of a Modern Problem*, 372 NEW ENG. J. MED. 1171, 1173–74 (2015).

135. See 21 U.S.C. § 352(n) (2012); see also Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 142 & n.6, 145–49 (1997).

136. See 15 U.S.C. § 52(a) (2012); *Sandoz Pharm. Corp. v. Richardson-Vicks, Inc.*, 902 F.2d 222, 227 (3d Cir. 1990) (“[T]he FDA regulates the labeling of OTC drugs while the FTC monitors the advertising for these drugs.”).

of the FDA.¹³⁷ Drug manufacturers contemplating a switch back to prescription status presumably would hesitate before again subjecting their marketing campaigns to the FDA's scrutiny.

Finally, to the extent that health insurers have become interested in advocating Rx-to-OTC switches,¹³⁸ which would lessen their covered charges for prescribed drugs and affiliated physician visits,¹³⁹ they would have no reason to want this process to work in the opposite direction.¹⁴⁰ Insofar as government payers offer drug benefits, their incentives presumably run parallel with those of private insurers.¹⁴¹ At the federal level, this means that the Centers for Medicare and Medicaid Services (CMS)—a sis-

137. See Jeremy A. Greene et al., Letter, *Changes in Direct-to-Consumer Pharmaceutical Advertising Following Shifts from Prescription-Only to Over-the-Counter Status*, 308 JAMA 973 (2012); Anne V. Maher & Lesley Fair, *The FTC's Regulation of Advertising*, 65 FOOD & DRUG L.J. 589, 602–03 (2010) (“For marketers accustomed to FDA’s regulatory approach, the FTC’s law enforcement framework may seem curious. Whereas FDA has promulgated detailed regulations relating to the advertising of prescription drugs, the FTC has promulgated no specific rules on the advertising of the health-related products for which it has primary responsibility.” (footnote omitted)); *id.* at 605–14 (discussing the Commission’s substantiation doctrine); see also Fisher, *supra* note 30, at 621–24 (describing decisions by the FTC against the adoption of sweeping restrictions on OTC drug advertising). Conversely, the Commission may impose more sweeping sanctions for regulatory infractions. See, e.g., *Novartis Corp. v. FTC*, 223 F.3d 783, 786–89 (D.C. Cir. 2000) (rejecting a challenge to a corrective advertising order for a nonprescription analgesic product); *FTC v. Pantron I Corp.*, 33 F.3d 1088, 1097–103 (9th Cir. 1994) (sustaining an enforcement action for false advertising against the seller of a baldness remedy); see also Maher & Fair, *supra*, at 614–22 (discussing the range of remedies available to the FTC).

138. See Spencer, *supra* note 131, at 1000–04 (providing background on an effort to have the FDA switch three nonsedating prescription antihistamines, and explaining that the agency never before had considered such a petition filed by an insurer and over the objections of the manufacturer); Leila Abboud, *Firms Gird for Drug-Cost Fight: FDA May Force Over-the-Counter Sales of Some Allergy Medicines*, WALL ST. J., May 6, 2003, at A4 (“Insurance companies—which don’t reimburse policyholders for over-the-counter medicines—love the idea of requiring that drugs be sold without prescriptions as much as pharmaceutical makers hate it . . .”).

139. See Spencer, *supra* note 131, at 1001–02 & n.12, 1021, 1026–29.

140. See Noah, *supra* note 11, at 361 (“If causing drowsiness made the older antihistamines more dangerous, then perhaps WellPoint [Health Networks, the parent company of Blue Cross and Blue Shield of California] should have urged the FDA to move them to prescription status or withdraw them from the market altogether. (Of course . . . that might have increased its tab for the [nonsedating] Rx products.)” (footnote omitted)).

141. See Rita Rubin, *FDA’s Push to Switch Antihistamines to Over-the-Counter Raises Eyebrows*, USA TODAY, Apr. 24, 2003, at 9D (“Now that the Bush administration has promised to add a prescription drug benefit to Medicare, some skeptics wonder whether the FDA is looking to save the government money by taking antihistamines out of the lineup of covered medications.”); see also Cohen et al., *supra* note 123, at 39 (doubting suggestions that a similar impetus accounted for the recent switch of a statin drug in the UK, but suggesting that it explains the switch of omeprazole in Sweden); Richard W. Stevenson, *Warner-Lambert in Two British Deals*, N.Y. TIMES, July 29, 1993, at D5 (noting a drug industry “belief that as governments look for ways to reduce health care costs, they will be quicker to approve nonprescription versions of drugs”).

ter agency of the FDA,¹⁴² which is also housed within the U.S. Department of Health and Human Services (HHS)—might well oppose any efforts to promote the public health by moving OTC drugs to prescription status because that would increase program costs. Indeed, contemporaneously with adoption of the Medicare drug benefit (Part D), the FDA's proposed FY2004 budget suggested that it would “become more proactive” in this area because Rx-to-OTC switches could “provide an expedient way to significantly reduce consumer health care costs.”¹⁴³

The incentives faced by patients/consumers point in varied directions.¹⁴⁴ For the uninsured, OTC availability offers clear benefits in terms of accessibility and affordability. For those with health insurance and comprehensive drug benefits (or else taking tax deductions for their medical expenses), prescription status may have somewhat greater appeal.¹⁴⁵ Nonetheless, even if an OTC switch at first confronts the latter group with higher out-of-pocket costs,¹⁴⁶ patients previously prescribed a drug will become accustomed to the convenience of purchasing these directly at retail.¹⁴⁷

142. See Lars Noah, *Coerced Participation in Clinical Trials: Conscripting Human Research Subjects*, 62 ADMIN. L. REV. 329, 333 n.16 (2010) (noting that “both agencies reside in the same cabinet-level department”).

143. Rita Rubin, *FDA Seeks to Switch Over-Counter*, USA TODAY, Apr. 23, 2003, at 1A (quoting language from the agency's proposed budget); see also Kaufman, *supra* note 21, at A1.

144. See Noah, *supra* note 11, at 377, 389 nn.154–55; Rook, *supra* note 52, at 100 (“At first glance, a drug's switch . . . may allow [the consumer] to avoid a doctor's appointment which would save time and money, and the OTC incarnation of the drug may cost less than its prescription version. However, our insurance and tax systems make the switch disadvantageous for many consumers.”).

145. See Rook, *supra* note 52, at 129 n.123 (“Relatively little data exists concerning the number of employer-provided plans that cover OTC medication, and there is virtually no explanation for why these drugs are almost never covered.”). Aside from differentials in insurance coverage, patients may claim a tax deduction for medical expenses, including uncovered expenses for prescription but not OTC drugs (except for insulin), now exceeding 10% of their adjusted gross income. See Tax Equity and Fiscal Responsibility Act of 1982, Pub. L. No. 97-248, § 202(b), 96 Stat. 324, 421 (codified as amended at 26 U.S.C.A. § 213(a)-(b) (2017)); see also Rook, *supra* note 52, at 137 n.165 (“Almost every state that imposes a sales tax exempts prescription drugs.”); Josh Barro, *The Latest Sales Tax Controversy: Tampons*, N.Y. TIMES, Jan. 7, 2016, at A3; cf. Sandra Block, *IRS Rulings Make Medical Flexible Spending Accounts More Attractive*, USA TODAY, Sept. 30, 2003, at 3B (reporting that employers now can offer “flex accounts” that would include purchases of OTC drugs among eligible expenses).

146. See Strom, *supra* note 11, at 1403 (explaining that after an Rx-to-OTC switch “patients with insurance that covers medications face the paradox of increased, rather than reduced, costs for their medications”); Milt Freudenheim, *Claritin's Price Falls, but Drug Costs More*, N.Y. TIMES, May 8, 2003, at C1; Christopher Rowland, *Over-the-Counter Versions Seen Raising Costs for Insured*, BOS. GLOBE, Jan. 31, 2004, at A1.

147. See Brass, *supra* note 11, at 812 (referencing significant increases in sales volume after an Rx-to-OTC switch).

In short, it seems unlikely that any of the potentially interested parties would want to press for unraveling an Rx-to-OTC switch. Unless the FDA takes seriously its public health mission and overlooks the hassles that it would encounter in moving a product back to prescription status—including likely objections from sponsors, insurers, consumers, and the various elected officials who represent the interests of these parties—this problem starts to appear largely intractable; deregulation then truly becomes a one-way ratchet.¹⁴⁸

B. *Awaiting Ad Hoc Fixes by State and Federal Legislatures*

By going back a century, one can find examples of drugs that moved from what amounted to OTC status into the category of prescription-only use, though these necessitated acts of Congress and hardly recommend themselves as successful experiments. For instance, in the course of implementing the Eighteenth Amendment to the U.S. Constitution,¹⁴⁹ Congress passed the Volstead Act,¹⁵⁰ which exempted from Prohibition alcoholic beverages when prescribed by a physician.¹⁵¹ Similarly, five years earlier, it effectively had moved opiates and cocaine into prescription status,¹⁵² and a few years after the repeal of Prohibition Congress did the same for marijuana.¹⁵³ Not until 1970 did it impose a blanket prohibi-

148. Cf. Colin Bradley & Alison Blenkinsopp, *Over-the-Counter Drugs: The Future for Self Medication*, 312 BRIT. MED. J. 835, 835–36 (1996) (repeatedly referring to Rx-to-OTC switches as “deregulation”). Strictly speaking, an Rx-to-OTC switch does not free a product from regulation, but it does remove restrictions on access.

149. U.S. CONST. amend. XVIII (1920), *repealed* by U.S. CONST. amend. XXI, § 2 (1933).

150. National Prohibition Act, Pub. L. No. 66–66, 41 Stat. 305 (1919), *repealed* by Pub. L. No. 74–347, 49 Stat. 872 (1935).

151. See *id.* tit. II, §§ 7–8, 41 Stat. at 310–11 (allowing for the medicinal use of certain liquors only when prescribed by a physician who had a special permit and only in strictly limited quantities); see also *Lambert v. Yellowley*, 272 U.S. 581, 589–97 (1926) (rejecting a constitutional challenge to this provision); cf. *James Everard’s Breweries v. Day*, 265 U.S. 545, 558–63 (1924) (upholding the affiliated prohibition against even purportedly medical uses of malt liquors); *id.* at 562 (“Congress determined, in effect, that intoxicating malt liquors possessed no substantial and essential medicinal properties which made it necessary that their use for medicinal purposes should be permitted . . .”).

152. See Harrison Narcotics Act, Pub. L. No. 63–223, §§ 2(a)&(b), 4, 38 Stat. 785, 786, 788 (1914) (repealed 1970); see also *Linder v. United States*, 268 U.S. 5, 17–23 (1925) (construing the statute narrowly so as not to intrude unduly on medical practice).

153. See Marihuana Tax Act, Pub. L. No. 75–238, § 2(a)(3), 50 Stat. 551, 552 (1937) (repealed 1970) (specifying an annual tax for health professionals who dispense, prescribe, or otherwise use this drug when treating their patients); *id.* § 6(b)(1)&(2), 50 Stat. at 553 (delegating authority to issue rules requiring maintenance of records in such cases); see also Noah, *supra* note 2, at 59 (pointing out that the *U.S. Pharmacopeia* “had listed marijuana as a drug for almost a century (until 1941), and prominent physicians had endorsed its use early in the twentieth century for treating maladies such as migraine headaches”).

tion on marijuana and certain other narcotics.¹⁵⁴ More recently, however, states began chipping away at the federal prohibition with medical marijuana initiatives,¹⁵⁵ which depended on securing some form of physician authorization.¹⁵⁶ Although federal law has not changed,¹⁵⁷ in some states marijuana now resides in what amounts to OTC status.¹⁵⁸

Contemporary responses to abused nonprescription drugs, at both the federal and state level, suggest a somewhat more nuanced approach to this problem. Concerns about methamphetamine have prompted legislators and retailers to restrict access to OTC cough-cold products containing the meth precursor pseudoephedrine.¹⁵⁹ In 2006, Congress dictated “behind-the-counter” status—though not limited to pharmacies—for products containing pseudoephedrine, but this statute sought to prevent

154. See Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91–513, tit. II, § 202(c), 84 Stat. 1236, 1248–49 (codified as amended at 21 U.S.C. § 812(c)) (listing marijuana in Schedule I(c)(10)); see also Noah, *supra* note 19, at 177, 180–82 (discussing the decision to place marijuana in Schedule I).

155. See Kevin P. Hill, *Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review*, 313 JAMA 2474, 2475 (2015) (“23 states and the District of Columbia have enacted medical marijuana laws to facilitate access to marijuana as a treatment for a variety of medical conditions.”); *id.* at 2476–77 tbl.1 (summarizing these various laws). See generally Todd Grabarsky, *Conflicting Federal and State Medical Marijuana Policies: A Threat to Cooperative Federalism*, 116 W. VA. L. REV. 1 (2013); Robert A. Mikos, *On the Limits of Supremacy: Medical Marijuana and the States’ Overlooked Power to Legalize Federal Crime*, 62 VAND. L. REV. 1421 (2009).

156. Some state laws avoid characterizing these as “prescriptions,” evidently to provide a bit of cover for health care professionals. See *Conant v. Walters*, 309 F.3d 629, 634–36 (9th Cir. 2002) (distinguishing physician “recommendation” required under California law from a “prescription”). For a discussion of initial and generally antagonistic federal responses to the earliest state initiatives, see Noah, *supra* note 19, at 151 & n.8, 181–83.

157. See Catherine Saint Louis, *D.E.A. Refusal to Reclassify Marijuana Draws Criticism*, N.Y. TIMES, Aug. 12, 2016, at A13. Congress recently (and only partially) relented. See Consolidated Appropriations Act of 2017, Pub. L. No. 115–31, § 537, 131 Stat. 135, 228 (providing that appropriations for the Department of Justice cannot be used to prevent the implementation of medical marijuana laws in 44 listed states and the District of Columbia); *United States v. McIntosh*, 833 F.3d 1163, 1169–70, 1176–79 (9th Cir. 2016) (applying earlier versions of this appropriations rider originally enacted in 2014).

158. See Paul Sullivan, *Investors Discovering Big Returns in Cannabis*, N.Y. TIMES, Jan. 27, 2018, at B3 (“Twenty-nine states now allow marijuana for medical purposes, while eight have legalized its recreational use.”). See generally Symposium, *One Toke Too Far? The Horizontal-Federalism Implications of Marijuana Legalization*, 58 B.C. L. REV. 857 (2017).

159. See Leslie Earnest & Rong-Gong Lin II, *Target Moves Sale of Cold Medications to Pharmacy*, L.A. TIMES, Apr. 19, 2005, at C1; Margaret Webb Pressler, *Retailers Restrict Some Cold Medicines: Ingredient Can Be Used to Make Meth*, WASH. POST, May 14, 2005, at A1. PPA also worked as a meth precursor, but the FDA urged the removal of this ingredient from OTC products on safety grounds at this same time. See *supra* notes 111–14 and accompanying text.

criminal diversion rather than any health risks to consumers.¹⁶⁰ In the face of continuing abuse, some states pursued stricter controls, including a couple that moved pseudoephedrine into prescription status.¹⁶¹ In the face of such access restrictions, several manufacturers of cough-cold products reformulated using phenylephrine.¹⁶² Retailers also have begun to limit access to other OTC cough-cold products in response to problems with teenagers purchasing them to get high.¹⁶³

Perhaps it would make sense to codify the notion of a pharmacist-controlled class of drugs to serve as a transitional step between prescription and OTC status when switching a new category of prescription pharmaceuticals.¹⁶⁴ Other industrialized countries use just such an intermediate category of products.¹⁶⁵ Although historically the FDA emphatically rejected proposals to create a “third class” of drugs,¹⁶⁶ more recently

160. See Combat Methamphetamine Epidemic Act of 2005, Pub. L. No. 109–177, tit. VII, § 711(b), 120 Stat. 256, 257–61 (2006) (codified as amended at 21 U.S.C. § 830); see also Note, *Cooking up Solutions to a Cooked up Menace: Responses to Methamphetamine in a Federal System*, 119 HARV. L. REV. 2508, 2517–18, 2524, 2526–27 (2006) (putting this law in context with earlier federal and state legislation). Indeed, the FDA had opposed the legislation, arguing that it inappropriately sacrificed the interests of consumers suffering from cold symptoms. See Gardiner Harris, *Fighting Methamphetamine, Lawmakers Reach Accord to Curb Sale of Cold Medicines*, N.Y. TIMES, Dec. 15, 2005, at A33.

161. See Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1, 20 & n.75; see also Christopher Wanjek, *Gee, Your Hair Smells Carcinogenic!; Why California Wants to Expose the Coal Tar in Dandruff Shampoos—And Why the Industry Is Resisting*, WASH. POST, Mar. 27, 2001, at T6 (“The [FDA] acknowledges that coal tar is carcinogenic but says that the over-the-counter coal-tar shampoos are safe But in California, . . . [activists and the state’s attorney general] are suing more than 20 manufacturers of coal-tar shampoos and ointments to require them to place warning labels on their products—and ultimately to sell them by prescription only.”).

162. See Jennifer Corbett Dooren, *Decongestants Get Makeover to Keep Them over the Counter*, WALL ST. J., May 9, 2006, at D3 (adding that this ingredient is somewhat less effective than pseudoephedrine).

163. See Rebecca Dana, *Household Medicine Abused by the Young; Trend Alarms Activists, Officials*, WASH. POST, Oct. 8, 2004, at A1 (highlighting “dextromethorphan, the active ingredient in cough medicines such as Robitussin”).

164. See Fisher, *supra* note 30, at 594 (“Recent ‘third class of drugs’ efforts have arisen primarily because of the FDA’s switch in recent years of many ingredients to ‘nonprescription’ status”); *id.* at 628 (concluding, however, that this would be unjustified); *Morning-After Pill May No Longer Need Prescription*, WALL ST. J., Nov. 25, 2003, at D4 (“[A]s OTC drugs evolve from quick symptom relief to more complex therapy, the FDA is considering whether it’s also time to change how some of them are sold, perhaps beginning ‘behind-the-counter’ sales for certain nonprescription drugs”).

165. See Fisher, *supra* note 30, at 625–26 (noting that the U.S. “is one of the few developed countries with only two classes of drugs,” but explaining that the European systems reflect peculiar customs and other factors unrelated to safety); see also Rita Rubin, *Rx out of the Box*, USA TODAY, Feb. 8, 2005, at 1D (“About half of non-prescription drugs in the United Kingdom can be sold only where pharmacists can supervise their sale”).

166. See *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 183 (E.D.N.Y. 2013); Final Order for Antacid and Antiflatulent Products Generally Recognized as Safe

it has suggested greater openness to the idea.¹⁶⁷ Most proponents of a behind-the-counter category view it as providing a transitional (or half) step from prescription to nonprescription status,¹⁶⁸ but, as the experience with pseudoephedrine demonstrates, it also may work in the opposite direction, offering a handy compromise for those stakeholders unwilling to move a drug entirely back into prescription status.¹⁶⁹

C. *Harnessing the Threat of Tort Liability to Drive Switchbacks*

When proceeding with an Rx-to-OTC switch, pharmaceutical manufacturers face increased exposure to tort liability,¹⁷⁰ both because patterns

and Effective and Not Misbranded, 39 Fed. Reg. 19,862, 19,864 (June 4, 1974) (“[T]here is no health or safety justification for establishing a third class of drugs at this time.”); OTC Drugs: Proposed General Conditions, 39 Fed. Reg. 19,880, 19,881 (June 4, 1974) (elaborating); U.S. CONG., GEN. ACCOUNTING OFFICE, PEMD-95-12, NONPRESCRIPTION DRUGS: VALUE OF A PHARMACIST-CONTROLLED CLASS HAS YET TO BE DEMONSTRATED, at 75–80 (1995) (concluding that little support exists for an intermediate class of drug products available only on the recommendation of pharmacists); Fisher, *supra* note 30, at 596 (“The federal government has often considered and has consistently rejected the establishment of a third class of drugs.”); *id.* at 596–604 (elaborating).

167. See Notice of Public Meeting, Behind the Counter Availability of Certain Drugs, 72 Fed. Reg. 56,769 (Oct. 4, 2007) (seeking input about the merits of this approach); see also Daniel Healey, *Plan BTC: The Case for a Third Class of Drugs in the United States*, 63 FOOD & DRUG L.J. 375, 378 (2008).

168. See Fisher, *supra* note 30, at 593, 601–04; *id.* at 628 (explaining that this “drives much of the current efforts by some to establish a third class of drugs”); Healey, *supra* note 167, at 377 & n.20, 388; *id.* at 379 (“BTC status could also provide a ‘testing ground’ to accumulate more safety data in preparation for a full-fledged OTC switch.”); *id.* at 384–85, 387 (focusing on cholesterol-lowering statins).

169. See Healey, *supra* note 167, at 378; McGinley, *supra* note 109, at A3 (quoting a medical expert as favoring behind-the-counter status for loperamide in the event that the FDA’s revised labeling and calls for more cumbersome packaging fail to guard against abuse of this antidiarrheal product). If pharmacists become responsible for the dispensing of formerly OTC drugs, then they would have a better chance of catching potential interactions with any prescription drugs used by a patient. Cf. Brass, *supra* note 11, at 814 (explaining that pharmacies do not track OTC purchases); Betsy Sleath et al., *Physician-Patient Communication About Over-the-Counter Medications*, 53 SOC. SCI. & MED. 357, 366 (2001) (“The trend toward prescription-to-OTC switches will make it increasingly important for patients to tell their physicians about their use of OTC medications, so . . . their providers can help prevent potential drug interactions and adverse effects from occurring.”); *id.* at 367 (“[I]ndividuals often fail to mention OTC products when they are asked what medications they are taking, possibly because they are unaware of potential adverse effects and/or drug interaction.”).

170. See Temin, *supra* note 7, at 353 (speculating that pharmaceutical manufacturers are not “anxious to increase their [liability] exposure by selling powerful drugs on the over-the-counter market”); *id.* at 356 (“[D]rug companies are exceedingly sensitive to the costs of being sued for the apparently negligent marketing of their products.”); Daniel W. Whitney, *Product Liability Issues for the Expanding OTC Drug Category*, 48 FOOD & DRUG L.J. 321, 349 (1993) (predicting that a switch to OTC status “may be accompanied by a greater frequency of personal injury claims”).

of consumption change in ways that present heightened risks of inappropriate use and because of differences in applicable products liability doctrine. For instance, courts typically apply a forgiving design defect standard to prescription drug products,¹⁷¹ while sellers of nonprescription drugs receive no special solicitude.¹⁷²

In addition, the learned intermediary doctrine, which substantially limits the availability of inadequate warning claims against sellers of prescription drugs by imposing a duty to warn only health care professionals, falls out of the picture.¹⁷³ When drug products can be purchased without a prescription, the manufacturer's duty to warn runs directly to consumers and requires that the information make sense to a layperson.¹⁷⁴ In making an Rx-to-OTC switch, the FDA invariably abridges the package insert, which means that some of the risk information previously communicated to physicians will not appear on the label of the nonprescription drug. When a consumer then experiences such a known but undisclosed side

171. See Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 842–84 (2009).

172. See, e.g., *Brown v. Johnson & Johnson*, 64 F. Supp. 3d 717, 721–23 (E.D. Pa. 2014) (rejecting the defendants' motion for summary judgment on claims that an OTC ibuprofen product intended for use in children suffered from a design defect because it allegedly was less safe than its enantiomer dexibuprofen, which the FDA previously had declined to approve but might do so if a sponsor conducted further testing); see also RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 2 cmt. k (1998). With regard to design defect claims, this makes sense because the *Restatement's* specialized standard asks whether a fully informed health care professional would select a prescription drug for any class of patients. See *id.* § 6(c); see also James A. Henderson, Jr. & Aaron D. Twerski, *Drug Designs Are Different*, 111 YALE L.J. 151, 156, 170–73, 178–79 (2001) (emphasizing physician involvement to justify the distinctive doctrinal treatment of prescription products); *id.* at 169 (“[S]uch differentiation [in design defect standards based on users] is not possible for nonprescription products, which are available to everyone on the open market.”). Some commentators have, however, questioned such second-class treatment for nonprescription products. See Noah, *supra* note 11, at 380 (“[T]hese protections also might extend to increasingly potent and useful nonprescription drugs. . . . In an earlier era, when OTC drugs offered marginal symptomatic relief and generally posed only trivial risks, it made sense to apply the same [design defect] standard used for cosmetics, appliances, and other consumer goods.”); Whitney, *supra* note 170, at 324 (“[I]t is difficult to fathom how a Rx drug would lose its social utility merely because it is being made available OTC.”).

173. See *Lofton v. McNeil Consumer & Specialty Pharm.*, 682 F. Supp. 2d 662, 679 (N.D. Tex. 2010) (“The court will not . . . apply this exception to an over-the-counter drug, even if at one time ibuprofen was a prescription drug.”); cf. Whitney, *supra* note 170, at 329–30 (arguing that the doctrine should remain applicable in cases where a doctor prescribes an OTC drug).

174. See, e.g., *O’Gilvie v. Int’l Playtex, Inc.*, 821 F.2d 1438, 1441–42 (10th Cir. 1987); *Hahn v. Sterling Drug, Inc.*, 805 F.2d 1480, 1482–83 (11th Cir. 1986); see also *Brown*, 64 F. Supp. 3d at 720–21 (rejecting the defendants' motion for summary judgment on claims that the manufacturer of an OTC ibuprofen product intended for use in children had failed to warn consumers of the risks of Stevens-Johnson Syndrome and toxic epidermal necrolysis, though concluding that there was no separate duty to warn physicians).

effect, the manufacturer may find itself hard-pressed to defend against a failure-to-warn claim.¹⁷⁵

As presently configured, therefore, tort law should make a pharmaceutical manufacturer think twice before switching a prescription drug to OTC status. Assuming, however, that a company has confidence in its product's relatively benign nature and the capacity for labeling to instruct laypersons about safe use, other incentives will weigh more heavily in favor of pursuing such a switch. Moreover, normal rules of causation would still apply and should protect manufacturers against liability claims for unsubstantiated side effects.¹⁷⁶ Finally, no liability should attach for failures to design against or warn of previously unknowable or rare risks such as allergic reactions.¹⁷⁷

What, however, if the risk-benefit balance sours at a later date? The FDA's failure to revisit its original assent to an Rx-to-OTC switch would not necessarily prevent plaintiffs from pressing design defect or inadequate warning claims,¹⁷⁸ and manufacturers would find it difficult to raise a federal preemption defense. Although Congress expressly displaced state regulation with respect to OTC drugs, it paired that provision with a clause saving tort claims.¹⁷⁹ This would not invariably foreclose invoking implied

175. See J. Warren Rissier, Note, *The FDA's Proposed Labeling Rules for Over-the-Counter Drugs and Preemption of State Tort Law*, 71 S. CAL. L. REV. 1387, 1399 (1998) ("OTC drug manufacturers are especially vulnerable to state tort lawsuits for failure to warn since 'switch' products will inevitably have fewer warnings on the OTC drug label than previously included on the prescription label."); *id.* at 1392, 1399–400 (elaborating on the reasons that labeling becomes abridged, and using the switched H₂ blocker Pepcid® to illustrate); see also Noah, *The Imperative to Warn*, *supra* note 34, at 338 (describing differences in consumer and professional labeling for otherwise identical drugs).

176. See, e.g., *Porter v. Whitehall Labs., Inc.*, 9 F.3d 607, 614–16 (7th Cir. 1993) (ibuprofen and kidney failure); *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1477–85 (D.V.I. 1994) (Primatene® and birth defects); *Burroughs Wellcome Co. v. Crye*, 907 S.W.2d 497, 499–500 (Tex. 1995) (reversing judgment for the plaintiff on failure-to-warn and related claims because of insufficient evidence that the OTC topical antibiotic spray Polysporin® caused frostbite injuries); *supra* note 111 (discussing the PPA litigation); see also *E.R. Squibb & Sons v. Cox*, 477 So. 2d 963, 970–71 (Ala. 1985) (holding that an insulin manufacturer's alleged failure to warn could not have caused any injury where the consumer admitted to discarding the product insert without reading it).

177. See, e.g., *Burlison v. Warner-Lambert Co.*, 842 F.2d 991 (8th Cir. 1988) (anaphylactic reaction to menthol in cough drops); *Daley v. McNeil Consumer Prods. Co.*, 164 F. Supp. 2d 367, 373–74 (S.D.N.Y. 2000) (Lactaid®); *Griggs v. Combe, Inc.*, 456 So. 2d 790, 792 (Ala. 1984) (reaction to benzocaine in Vagisil®).

178. See Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 GEO. L.J. 2147, 2150–52, 2155–58 (2000) (explaining that satisfying FDA requirements generally does not serve as a defense).

179. See 21 U.S.C. § 379r (2012); *Over-the-Counter Drugs: Labeling Requirements*, 64 Fed. Reg. 13,254, 13,272 (Mar. 17, 1999); cf. *Green v. BDI Pharm.*, 803 So. 2d 68, 74–75 (La. Ct. App. 2001) (finding express preemption of a failure-to-warn claim involving an OTC ephedrine product, ignoring entirely the impact of the savings clause). Because the preemption provision applicable to medical devices did not include a savings clause, courts find express preemption of tort

preemption,¹⁸⁰ but the U.S. Supreme Court has largely refused to allow such a defense against failure-to-warn claims involving drugs with approved NDAs because an FDA regulation allows unilateral revisions to risk labeling by the brand-name company holding such a license.¹⁸¹ Preemption aside, manufacturers might come to miss the relative shelter from expansive products liability claims reserved for prescription drugs and consider seeking a return to that status.

Moreover, even if they encountered obstacles to asserting design defect and failure-to-warn claims against manufacturers of OTC drugs that caused injury, plaintiffs might try to pursue a “negligent marketing” claim.¹⁸² Although this theory of liability remains largely untested, it may

claims, *see* *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 322–30 (2008), including those brought against devices sold directly to consumers, *see, e.g.*, *Papike v. Tambrands, Inc.*, 107 F.3d 737, 740–42 (9th Cir. 1997) (tampons); *Murphy v. Playtex Fam. Prods. Corp.*, 176 F. Supp. 2d 473, 482–83 (D. Md. 2001) (same), *aff’d*, 69 F. App’x 140 (4th Cir. 2003) (per curiam); *cf.* *Buckman v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 347–53 (2001) (finding a fraud-on-the-FDA claim involving review of a medical device impliedly preempted). In contrast, Congress has largely remained silent about preemption with respect to prescription drugs. *See* Noah, *supra* note 161, at 8–9.

180. An effort to use California’s Proposition 65, which Congress also had saved from the operation of the express preemption clause, to require reproductive toxicity warnings on OTC smoking cessation products foundered on the basis of implied preemption because it would frustrate the purposes underlying the FDA’s decision not to mention this risk. *See* *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 9–11, 15 (Cal. 2004); *see also* Sandhya Somashekhar, *Smoking-Cessation Restrictions to Be Eased*, WASH. POST, Apr. 2, 2013, at A2 (reporting that, at the urging of public health advocates and in order to encourage efforts to quit, the FDA further watered down the instructions for guarding against nicotine overdose).

181. *See* *Wyeth v. Levine*, 555 U.S. 555, 567–81 (2009); *see also* *Reckis v. Johnson & Johnson*, 28 N.E.3d 445, 455–61 (Mass. 2015) (rejecting an implied preemption defense to claims that the manufacturer of an OTC ibuprofen product had failed to warn consumers of the risks of Stevens-Johnson Syndrome and toxic epidermal necrolysis). Implied preemption should, however, bar design defect claims against manufacturers of FDA-approved drugs. *See* Noah, *supra* note 161, at 29–34. Furthermore, implied preemption might also defeat failure-to-warn claims involving OTC drugs governed by monographs as opposed to NDAs—after all, under these classwide regulations, the FDA (rather than any particular sponsor) dictates the precise content of labeling and allows essentially no deviations. *See* 21 C.F.R. § 330.1(c)(2)(i), (j) (2018); *see also* Noah, *The Imperative to Warn*, *supra* note 34, at 321 (“Even when it revised its policy to allow for greater flexibility in labeling, FDA continued to demand verbatim adherence to any warnings prescribed in the regulations.”).

182. *See* Lars Noah, *Platitudes About “Product Stewardship” in Torts: Continuing Drug Research and Education*, 15 MICH. TELECOMM. & TECH. L. REV. 359, 385–91 (2009); *cf.* Richard C. Ausness, *Tort Liability for the Sale of Non-Defective Products: An Analysis and Critique of the Concept of Negligent Marketing*, 53 S.C. L. REV. 907, 909–10, 915–16, 944–46 (2002); *id.* at 939 (“Just a few years ago, it appeared that negligent marketing was about to become a powerful tool in products liability litigation, particularly where the products involved were not ‘defective’ in the traditional sense.”); *id.* at 965 (concluding for a variety of reasons that courts should decline to recognize such claims).

help to provide the impetus needed to overcome the absence of other incentives to unravel a switch. If an OTC drug with otherwise unassailable design and labeling causes an injury, then the victim might argue that the product should have been made available only under professional medical supervision and never sold directly to consumers.¹⁸³ Such a claim would represent something of a hybrid between more traditional defects in design and labeling, challenging a manufacturer's choice about the appropriate channels for distributing potentially hazardous goods, such as items not appropriate for use by youngsters,¹⁸⁴ in a way that resembles novel (and so far largely unsuccessful) theories asserted against gun manufacturers.¹⁸⁵ In particular, such claims find their closest parallel in lawsuits alleging that manufacturers of certain types of weapons or ammunition should not have sold these products to civilians, instead limiting their distribution to law-enforcement professionals and the military.¹⁸⁶

183. See Howard Latin, "Good" Warnings, Bad Products, and Cognitive Limitations, 41 UCLA L. REV. 1193, 1271 (1994) ("Why should the presence of a 'good' warning, no matter how explicit, prevent courts from considering the value of alternative marketing strategies in light of the common tendency of people to overuse over-the-counter drugs that provide relief from chronic ailments?"); Whitney, *supra* note 170, at 328–29 (speculating, without further elaboration, that consumers injured by a nonprescription drug may argue that it "was so dangerous no warning would be sufficient" and that "the drug should not be available OTC because of the need for supervision and control by a qualified physician"); see also Michael v. Warner/Chilcott, 579 P.2d 183, 189–90 (N.M. Ct. App. 1978) (Hernandez, J., concurring) (concluding that, although no reasonable jury could have found an inadequacy in the warning of kidney damage from prolonged use of a decongestant product containing phenacetin, the plaintiff's expert testimony that this drug should have been restricted to prescription status provided sufficient evidence to support his design defect claim); cf. Ramirez v. Plough, Inc., 863 P.2d 167, 177–78 (Cal. 1993) (rejecting the plaintiff's claim that the defendant should not have marketed OTC children's aspirin because of the risk of Reye's syndrome and the availability of safer substitutes).

184. See, e.g., Moning v. Alfonso, 254 N.W.2d 759, 762 (Mich. 1977) (holding that a jury should resolve negligence claims against the manufacturer, wholesaler and retailer of slingshots marketed directly to children); *id.* at 771 ("The issue in the instant case is not whether slingshots should be manufactured, but the narrower question of whether marketing slingshots directly to children creates an unreasonable risk of harm."); cf. First Nat'l Bank of Dwight v. Regent Sports Corp., 803 F.2d 1431, 1435 (7th Cir. 1986) (rejecting failure-to-warn and negligent marketing claims against the manufacturer of metal-tipped lawn darts sold as appropriate for adults only, but allowing claims for violations of federal regulations prohibiting sales of such products through toy stores and similar retail outlets).

185. See, e.g., Merrill v. Navegar, Inc., 28 P.3d 116, 119 (Cal. 2001); Chicago v. Beretta U.S.A. Corp., 821 N.E.2d 1099, 1148 (Ill. 2004); Hamilton v. Beretta U.S.A. Corp., 750 N.E.2d 1055, 1059 (N.Y. 2001); see also Jean Macchiaroli Eggen & John G. Culhane, *Gun Torts: Defining a Cause of Action for Victims in Suits Against Gun Manufacturers*, 81 N.C. L. REV. 115, 204–09 (2002). But see Iletto v. Glock Inc., 349 F.3d 1191, 1201–09 (9th Cir. 2003) (allowing a negligent marketing claim to proceed); City of Cincinnati v. Beretta U.S.A. Corp., 768 N.E.2d 1136, 1141 (Ohio 2002) (allowing a municipality to pursue such claims).

186. See, e.g., McCarthy v. Olin Corp., 119 F.3d 148, 152, 156–57 (2d Cir. 1997) (noting, in the course of rejecting such a claim, that the manufacturer of Black Talon ammunition subsequently limited sales to professionals); *id.* at 163

Even if the FDA had approved an Rx-to-OTC switch, an injured consumer might argue that a reasonable drug manufacturer should never have undertaken marketing directly to laypersons. If confronted with the response that it would violate federal law to sell an OTC drug product with prescription-only labeling,¹⁸⁷ a plaintiff instead might argue that the manufacturer acted negligently in failing to request that the agency allow it to switch a dangerous drug to prescription status. Nonetheless, unlike other revisions of labeling that the manufacturer of an FDA-approved drug might undertake unilaterally, the fact that such a switch in status would necessitate waiting for the agency's permission should bar liability for negligent marketing on grounds of implied federal preemption.¹⁸⁸ Thus, even if courts seemed otherwise receptive to this novel theory, plaintiffs would have to find some way of getting around preemption before tort law offers much help in encouraging manufacturers to think seriously about switching OTC products back to prescription status.

Finally, retailers also may face enhanced exposure to liability after an Rx-to-OTC switch. Pharmacists encounter only limited liability in selling prescription products, but pharmacies and other businesses that sell non-prescription drugs face the same strict liability imposed on retailers of regular consumer goods.¹⁸⁹ Indeed, retailers enjoy greater flexibility than OTC drug manufacturers when it comes to restricting consumer access to such products, as demonstrated by chains that opted for behind-the-counter sales of drugs containing pseudoephedrine before that became mandatory.¹⁹⁰ Thus, if they fail to adopt such point-of-purchase safeguards, then this class of potential defendants may face negligent marketing claims, and they would not get the benefit of an implied preemption defense because the FDA hardly exercises any control over nonprescription drug product retailers.

V. CONCLUSION

Once a prescription drug has transitioned into the nonprescription marketplace, a variety of factors conspire against moving it back. Instead, as worrisome additional hazards of use come to light, the FDA simply

(Calabresi, J., dissenting) ("Selling tanks to the armed forces is fine; selling them to the general public is, I would think, clearly negligent.").

187. See 21 U.S.C. § 353(b)(4)(B) (2012); 21 C.F.R. § 310.200(d) (2018).

188. See *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 484–87, 490–92 (2013).

189. See, e.g., *Morales v. Am. Home Prods. Corp.*, 214 F. Supp. 2d 723, 726 (S.D. Tex. 2002); see also RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(e) & cmt. h (1998); David J. Marchitelli, Annotation, *Liability of Pharmacist Who Accurately Fills Prescription for Harm Resulting to User*, 44 A.L.R.5th 393 (1996 & 2017 Supp.).

190. See *supra* note 159 and accompanying text; see also Joyce Gemperlein, *Ask the Pharmacists: Why Are Nonprescription Items Behind the Counter?*, WASH. POST, Dec. 25, 2005, at Z6. Only once before has the manufacturer of an OTC drug tried to create (and then only temporarily) a behind-the-counter system of distribution. See Francesca Lunzer Kritz, *Over the Counter but Not Easy to Reach*, WASH. POST, Oct. 8, 2002, at F3 (Mucinex® (guaifenesin)).

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shares the new risk information with consumers. In spite of evidence that laypersons pay little or no attention to such disclosures, and the mounting injuries suffered by consumers, the agency persists in its unproductive strategy of larding up product labels rather than reconsidering the wisdom of its original judgment to authorize OTC availability.¹⁹¹ This represents a serious public health problem that deserves more than the passing attention it has received to date. Although tort litigation might serve as a partial counterweight to manufacturers' lack of incentives to request a return to prescription status, judicial resistance to negligent marketing claims coupled with receptivity to the preemption defense severely limit this prospect. In the absence of a greater willingness by the FDA to confront this issue (or some sort of broad-based legislative reforms designed to facilitate such a process), the dangers associated with giving consumers largely unsupervised access to powerful pharmaceutical agents have become largely intractable.

191. Cf. Noah, *The Imperative to Warn*, *supra* note 34, at 398 ("If the goal is to influence behavior and deter use of a product without entirely constraining freedom of choice, alternatives to labeling might include . . . prescription requirements of different stringency.").

