

EMERGENT REGULATORY SYSTEMS AND THEIR CHALLENGES: THE CASE OF COMBINATION MEDICAL PRODUCTS

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Abstract: Where regulatory systems overlap, courts and scholars often focus on the undesirable aspects of the overlap—the ways in which systems conflict. One such context involves the regulation of prescription drugs and medical devices by the FDA’s premarket evaluation processes and by state common-law tort and products liability actions. FDA regulation and state common law are often described as separate, conflicting regulatory systems. This Article challenges that description by proposing a model in which FDA premarket evaluation and state common law function as a single regulatory system.

This model brings order to the Supreme Court’s seemingly inconsistent medical products preemption cases, permitting the Court’s decisions in *Medtronic v. Lohr*, *Riegel v. Medtronic*, *Wyeth v. Levine*, *PLIVA v. Mensing*, and other cases to be understood as having created an emergent, coherent, multilayered regulatory system that calibrates the requirements imposed by each layer to the deficit in information about the risk of each product category. The model also provides a strong critique of scores of recent lower court preemption decisions involving “combination products,” a new product category whose members consist of both a new drug and a high-risk device. In finding common law actions preempted, these courts claim to have faithfully applied *Riegel*’s holding. But using the model developed here, it is clear that courts have disrupted the calibrated regulatory system, allowing thousands or millions of people in the United States to be exposed to dangerous products whose risks have not been well-characterized. Using the combination products decisions as a cases study, the model also highlights the far-reaching effects that even small changes to any one input may have on the function of an emergent system and the field that it regulates.

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INTRODUCTION

A crucial challenge for products regulation is how to adequately ensure safety (and in some contexts, effectiveness) while limiting the adverse impacts of regulation on the development of and timely access to beneficial new technologies. Perhaps nowhere are the tensions between these goals as salient as in the regulation of medical products. New prescription drugs, medical devices, and biologics contributed to a 50%

decline in annual mortality¹ and a twenty-nine-year increase in life expectancy in the United States during the twentieth century.² But these products also injure or kill well over a million people in the United States each year.³ Quite literally, our lives depend on striking a balance between the competing objectives of ensuring safety, effectiveness, product development, and access.

Understanding how any one regulatory system balances such competing objectives is a challenge. Understanding how multiple systems combine to balance competing objectives is even more challenging, but can provide important insights for scholars, regulators, the regulated entities, and those whom regulation is meant to protect. Medical products are regulated through the Food and Drug Administration's (FDA) premarket evaluation pathways, the FDA's post-market authorities, passive reporting requirements, state tort and products liability law, and a host of other formal and informal mechanisms. Courts and scholars often focus on just one of these regulatory inputs.⁴ Decisions and accounts that focus on two of the inputs tend to emphasize the conflicting obligations the inputs may impose on manufacturers.⁵ Courts, by the case-specific

1. See U.S. CENSUS BUREAU, STATISTICAL ABSTRACT OF THE UNITED STATES: 1999, at 874 tbl. 1420 (1999), <https://www.census.gov/prod/99pubs/99statab/sec31.pdf> [<https://perma.cc/YE9E-FXRK>] (reporting a death rate per 1,000 people per year in 1900 of 17.2 and in 1997 of 8.6).

2. *Id.*

3. See *A Delicate Balance: FDA and the Reform of the Medical Device Approval Process: Hearing Before the Spec. Comm. on Aging*, 112th Cong. 67, 68 (2011) (statement of Diana Zuckerman) (noting that over 500,000 metal-on-metal hip prostheses implanted into Americans are prone to breakdowns that cause pain, decreased mobility, lost work, repeat surgeries, post-operative rehabilitation, and other costly sequelae); Marcia Boumil, *FDA Approval of Drugs and Devices: Preemption of State Laws for "Parallel" Tort Claims*, 18 J. HEALTH CARE L. & POL'Y 1, 6 (2015) (citing estimates of over 100,000 deaths in the United States related to prescription drugs and medical devices); JUDITH A. JOHNSON, CONG. RESEARCH SERV., *FDA REGULATION OF MEDICAL DEVICES* 3 (2016) [hereinafter JOHNSON 2016], <https://fas.org/sgp/crs/misc/R42130.pdf> [<https://perma.cc/S8N2-6N7M>] (citing FDA report of 116,086 device-related injuries and an independent analysis concluding there were 4,556 device-related deaths in one recent year); Justin M. Mann, *FDA Adverse Event Reporting System: Recruiting Doctors to Make Surveillance a Little Less Passive*, 70 FOOD & DRUG L.J. 371, 381 (2015) (citing 2013 data that 1.1 million voluntary reports of injuries and death were submitted to the FDA's Adverse Event Reporting System (FAERS)); Thomas J. Moore, Michael R. Cohen & Curt D. Furberg, *Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005*, 167 ARCH. INTERN. MED. 1752, 1754 (2007) (stating that roughly one-sixth of FAERS reports were for deaths).

4. See, e.g., *Prevor v. FDA*, 895 F. Supp. 2d 90, 98 (D.D.C. 2012) (discussing FDA premarket regulation); Susan B. Foote & Robert J. Berlin, *Can Regulation be as Innovative as Science and Technology? The FDA's Regulation of Combination Products*, 6 MINN. J.L. SCI. & TECH. 619 (2005) (discussing the same).

5. See *infra* sections I.B and I.D.

nature of their authority, and scholars, by self-imposed scope restrictions, typically focus on a single product or a product category.⁶

This Article seeks to answer several questions. How do the individual systems that regulate all prescription medical products function together? Can the combined function of these systems be described as a coherent system? And most importantly, what balance between safety, effectiveness, product development, and timely access does the combined function strike?

The first step in this inquiry is to define the scope of the regulated entity, as many products offer health benefits and pose health risks. The next step is to establish and prioritize the goals that regulation of the chosen entity is to achieve. Then it is necessary to identify the relevant individual regulatory inputs. Regulation is rarely achieved by a single body. More commonly, multiple regulatory inputs influence the activities of the regulated entity. Finally, and most difficult, it is necessary to understand how these inputs function together. The individual regulatory inputs may seek different policy goals or prioritize the same set of goals differently. The combined effect of the inputs may differ from the effects of any individual input.

This Article limits its scope to prescription drugs, medical devices, biologics, and so-called “combination products,” which combine two or more of these categories. Although a much wider range of products affect human health,⁷ this Article focuses on those products that provide the greatest benefits and pose the greatest risks, and those that are among the most heavily regulated on the U.S. market. The Article recognizes the goals of ensuring effectiveness, fostering development, and allowing timely access to newly developed products.⁸ But both descriptively and

6. See, e.g., *Riegel v. Medtronic, Inc.*, 552 U.S. 312 (2008) (focusing on medical devices); *Wyeth v. Levine*, 555 U.S. 555 (2008) (focusing on prescription drugs); Mann, *supra* note 3 (focusing on prescription drugs). *But see* Boumil, *supra* note 3 (focusing on prescription drugs and medical devices).

7. The FDA regulates many other products that may have health effects, including cosmetics, over-the-counter drugs, foods, animal drugs, and nutritional supplements. Tort and products liability law regulate an even wider range of products that may affect health.

8. See 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2015) (strengthening and extending application of least burdensome principle); FDA Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (establishing the least burdensome principle for device regulation); Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (creating Abbreviated New Drug Approval pathway for generic drugs); Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (creating a Section 510(k) substantial equivalence pathway for intermediate risk devices).

normatively, this Article views ensuring safety as the primary goal of medical product regulation.⁹

Two major regulatory inputs for medical products are federal premarket evaluation by the FDA and state tort and products liability law.¹⁰ The FDA's premarket evaluation involves determining whether the overall benefits to the public associated with the use of a product outweigh the risks that come with the use of that product.¹¹ State tort and products liability cases require determining whether a manufacturer acted reasonably to prevent harm to injured individuals—that is, whether the manufacturer reasonably ensured safety in view of the risks created by the product.¹² These two inputs are often viewed as inherently conflicting.¹³ State law may stand as an obstacle to the objectives of federal regulation, particularly the goal of fostering development and access through the creation of a uniform, nationwide regulatory regime.¹⁴ And federal regulation of drugs and devices may establish both a regulatory floor and ceiling, preempting state regulation.¹⁵

9. See 21 U.S.C. § 393(b)(2) (2012) (establishing the role of the FDA as being “[to] protect the public health by ensuring that . . . human . . . drugs are safe and effective [and that] there is reasonable assurance of the safety and effectiveness of devices intended for human use”); see also Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (amending the Food, Drug, and Cosmetic Act “to provide for the safety and effectiveness of medical devices intended for human use”); Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (“An [a]ct [t]o protect the public health”); Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906), *repealed by* Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (prohibiting sale of “adulterated or misbranded or poisonous or deleterious . . . drugs [and] medicines”); *Id.* (prohibiting interstate movement of misbranded and adulterated drugs and devices).

10. Catherine M. Sharkey, *States Versus FDA*, 83 GEO. WASH. L. REV. 1609, 1611 (2015). Other regulatory inputs include the FDA's post-market authorities, industry-created standards, market forces, and prescriber decisions. See *infra* Part V.

11. 21 U.S.C. § 355(d) (2012) (requiring that new drug approval process must utilize “a structured risk-benefit assessment”); 21 U.S.C. § 360e(d)(1)(A) (2012) (stating that standard for approval of high-risk medical device is “a reasonable assurance of safety and effectiveness”).

12. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 2(b)–(c) (Am. Law. Inst. 1998) (providing that standard for products liability design defect and failure to warn met where omission of reasonable alternative design or reasonable instructions or warnings “renders the product not reasonably safe”).

13. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims*, 96 GEO. L.J. 461, 463–64 (2008).

14. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 326 (2008) (noting the likely effects on innovation “if juries were allowed to apply the tort law of 50 States to all innovations”).

15. William W. Buzbee, *Federal Floors, Ceilings, and the Benefits of Federalism's Institutional Diversity*, in PREEMPTION CHOICE: THE THEORY, LAW, AND REALITY OF FEDERALISM'S CORE QUESTION 98 (William W. Buzbee ed., 2009). Preemption may leave injured patients with recourse against the manufacturer and limited means of obtaining compensation. *Riegel*, 552 U.S. at 333 (Ginsburg, J., dissenting) (discussing how preemption “effect[s] a radical curtailment of state common-law suits seeking compensation”); *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 643 (2011)

This Article begins in Part I by articulating a different view: that although federal premarket approval and state tort and products liability law are separate regulatory inputs, together they form an emergent, functionally unified, coherent system that imposes a calibrated set of obligations on manufacturers to produce and disseminate information about product risk. This calibrated system has only fully emerged with the Supreme Court's recent preemption decisions in cases involving prescription drugs and medical devices.¹⁶ But the calibration itself reflects certain mid-twentieth century understandings of drugs and devices.

In the early to mid-twentieth century, most drugs were “discovered” in nature.¹⁷ Because information about drug structure, drug function, and human biochemistry was limited, the therapeutic and adverse effects of new drugs could only be characterized by exposing large numbers of humans to them.¹⁸ By contrast, in the mid- to late-twentieth century devices were created by “design.”¹⁹ Their components and the site and nature of their actions were known in advance; hence their risks were thought to be predictable.²⁰

Consistent with the large information deficit about new drug risk, the current regulatory system for drugs uses a two-layered approach that forces the production of large amounts of information about the risks of new drugs. The federal premarket New Drug Application (NDA) process provides the first layer. Although this process is the most rigorous evaluative process to which medical products are subjected,²¹ it cannot identify all significant new drug risks.²² State tort and products liability

(Sotomayor, J., dissenting) (discussing how preemption “strips generic-drug consumers of compensation when they are injured by inadequate warnings”).

16. The most recent of these cases was *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 570 U.S. 472 (2013). See *infra* section I.B.

17. See Editorial, *Looking Back on the Millennium in Medicine*, 342 *NEW ENG. J. MED.* 42, 47 (2000) [hereinafter *Looking Back*].

18. DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* 145–46 (2010) (describing mid-century clinical pharmacologists' attitude “that only long-term animal studies and controlled clinical trials could permit an accurate assessment of the efficacy and safety of drugs new and old”).

19. See Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § Sec. 201(h), 52 Stat. 1040, 1041 (defining “device” as “instruments, apparatus, and contrivances”).

20. For a more recent statement of this assumption, see FDA, *DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF, CONSIDERATION OF UNCERTAINTY IN MAKING BENEFIT-RISK DETERMINATIONS IN MEDICAL DEVICE PREMARKET APPROVALS, DE NOVO CLASSIFICATIONS, AND HUMANITARIAN DEVICE EXEMPTIONS* 5 (2018) (“[T]he mechanism of action and modes of failure are generally more predictable and better understood for devices than for drugs and biological products.”).

21. See *infra* section I.A.

22. See, e.g., Boumil, *supra* note 3, at 6 (citing estimates that over 10% of FDA approved drugs

law serves as a second layer that forces the generation and dissemination of additional risk information as very large numbers of people encounter a new drug.²³

The highest-risk devices must be approved through the federal Premarket Approval (PMA) process.²⁴ Although courts and others typically emphasize the rigorous nature of the PMA process,²⁵ it is less rigorous than the NDA process for new drugs.²⁶ But consistent with the view that device risks are predictable, once the FDA is satisfied that a reasonable assurance of safety has been provided, state-level information-forcing would provide little additional risk information. And indeed, high-risk medical device regulation relies on a single-layered approach, with state law actions preempted by FDA regulation.

Sections I.A and I.B detail the federal and state layers of regulation, respectively. Section I.C then advances the descriptive and normative starting point for this Article, which is that these independent regulatory inputs—federal and state regulation of drugs and devices—function as a single system that forces manufacturers to generate and disclose information about product risk.²⁷ This system is emergent, in that none of the individual regulatory inputs, including four distinct federal premarket processes,²⁸ state tort and products liability law,²⁹ and the Supreme Court’s medical products preemption decisions,³⁰ were designed to create an overarching system that calibrates information-producing obligations to the information deficits that exist for all of the product categories. Rather, the calibrated function of the system emerges from the interactions of these different regulatory inputs. This descriptive account provides the normative position taken in the remainder of this Article: that

were subsequently found to have a safety risk severe enough to require a “black box” warning or market withdrawal).

23. *Wyeth v. Levine*, 555 U.S. 555, 579 (2008) (noting FDA’s earlier position that state law provides an additional layer of protection against drug risks); Sharkey, *States Versus FDA*, *supra* note 10, at 1613.

24. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 317 (2008).

25. *See, e.g., id.* at 317 (“Premarket approval is a ‘rigorous’ process.” (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 477 (1996))).

26. *See infra* section I.A.

27. *See*; Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623, 628–29 (2007); Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS 117, 138 (2016) (describing FDA premarket evaluation and state common law interactions as “encouraging the production and distribution of information”).

28. *See infra* section I.A.

29. *See infra* section I.B.

30. *See infra* section I.D.

the quantity and quality of information required of a medical product should be directly proportional to how difficult it is for scientists, regulators, prescribers, and patients to predict the risks posed by that product. Section I.D discusses the Supreme Court's pivotal role in creating this system.

But almost as soon as the calibrated system of information generating and disclosure obligations emerged, lower court decisions in cases involving "combination products"—particularly products made up of a new drug and a high-risk device³¹—threatened to subvert the system. Manufacturers can gain FDA approval for some new drugs through the less rigorous PMA process by submitting the new drug as a constituent of a combination product.³² The resulting information deficit might be partially offset by state tort and products liability law actions. But courts have largely eliminated this second, post-market layer by finding state products liability actions in combination products cases to be preempted.³³ The resulting regulatory gap diminishes the safety of a large and rapidly growing category of medical products.

Part II describes this challenge to the calibrated regulatory system for medical products. Section II.A provides an introduction to combination products. By industry estimates, as many as one-third of all new products in development are combination products.³⁴ Unfortunately, predicting the risk of drug-device combination products is often more difficult than predicting the risks of new drugs or high-risk devices. Section II.B illustrates the regulatory gap, focusing on one extensive line of cases stemming from thousands of injuries related to a drug-device combination product used in spinal surgery. Section II.B concludes that the rise of combination products and the creation of the regulatory gap may alter the overall system of medical product regulation such that it no longer calibrates information generating and disclosing obligations to risk information deficits. In effect, a new regulatory system, which sacrifices some of the normative advantages of the existing system, may be emerging.

To illustrate this change, Part III examines the immediate causes of the regulatory gap. Section III.A explains how Congress created the federal

31. "Combination products" are defined as products that consist of more than one product type, that is, some combination of a drug and device, a biologic and a device, a drug and a biologic, or a drug and a device and a biologic. 21 U.S.C. § 353(g) (2012); 21 C.F.R. § 3.2(e) (2019).

32. See *infra* section I.A.

33. See *infra* section I.B.

34. Michael Drues, *Combination Products 101: A Primer For Medical Device Makers*, MED DEVICE ONLINE (Mar. 25, 2014), <https://www.meddeviceonline.com/doc/combination-products-a-primer-for-medical-device-makers-0001> [<https://perma.cc/NA6N-HQSL>].

side of the gap by crafting a regulatory regime for combination products that allows manufacturers to gain FDA approval of certain new drugs through the PMA process. By itself, this did not represent a serious threat to the calibrated system described in Part I. But in recent years the lower federal and state courts have held that state tort and products liability claims are preempted in a growing number of cases. Section III.B presents the first comprehensive review of court decisions in cases involving drug-device combination products to analyze the approach that courts have taken in determining the preemptive effect of FDA regulation. This section argues that most courts' preemption analyses have relied on three unwarranted assumptions about the proper construction of the term "combination products" and about the preemptive reach of federal regulation of medical devices. Section III.C offers some tentative explanations for why courts have failed to examine the premises that underlie these assumptions.

Part IV explores whether the regulatory gap could be closed, and concomitantly whether the existing emergent system of regulation can be preserved. On the federal side, the FDA retains sufficient statutory authority to channel more combination product approvals through the new drug pathway and to demand greater rigor in pivotal trials used to support approvals under the device pathway. But a number of ethical and practical considerations will limit the impact of these options. On the state side, courts could under existing statute, regulation, and Supreme Court precedent find fewer cases preempted, allowing state law to function as it does in cases of injury involving FDA-approved new drugs. But at most these moves can only narrow, not fully close, the gap. Thus, the emergent regulatory system described in Part I may prove to be ephemeral.

Finally, in Part V, this Article returns to the view of medical products regulation as an emergent system. By viewing the distinct regulatory inputs as a single, emergent system, seemingly bizarre features of any single input may be understood as serving a rational function. This approach also emphasizes the far-reaching effects that even small changes to any one input may have on the function of the emergent system. This way of viewing regulatory inputs also aligns with the views of the regulated entities, which are subjected to all of the inputs. The main challenge to this approach is its sensitivity to initial choices, such as which regulatory inputs are most relevant.

I. MEDICAL PRODUCTS REGULATION

Regulating medical products requires finding an optimal balance between the often-competing policy objectives of assuring safety,

efficacy, innovation, and access.³⁵ Over the course of the twentieth century, the development of new prescription drugs, medical devices, and biologics contributed to a fifty percent decline in mortality rates³⁶ and to a twenty-nine-year increase in life expectancy in the United States.³⁷ But injuries and deaths resulting from these products are widespread and costly.³⁸ Medical devices injure or kill well over 100,000 people in the United States each year.³⁹ In 2013, prescription drug use resulted in more than 1.1 million voluntary reports to the FDA's Adverse Event Reporting System.⁴⁰ One-sixth of these reports are deaths.⁴¹ And these numbers likely underestimate the harms caused by medical products: empirical evidence suggests that most serious adverse events go unreported.⁴²

One way to ensure safety would be to subject every new medical product to a maximally rigorous assessment before the product is marketed and to continuous close monitoring afterward. But other policy considerations weigh against such extensive regulation. The costs imposed by premarket review can discourage manufacturers from engaging in the research and development necessary to create new, potentially life-saving products.⁴³ And extensive premarket review can delay patients' access to newly-developed products.⁴⁴ Further, post-market liability under state common law can drive FDA-approved,

35. Robert M. Califf, *Benefit-Risk Assessments at the U.S. Food and Drug Administration*, 317 JAMA 693 (2017).

36. See U.S. CENSUS BUREAU, *supra* note 1, at 874 tbl.1420.

37. *Id.* at 874, tbl.1421.

38. See Boumil, *supra* note 3, at 6.

39. JOHNSON 2016, *supra* note 3, at 3.

40. See, e.g., Boumil, *supra* note 3, at 6; Mann, *supra* note 3, at 381 (citing 2013 data).

41. Moore, Cohen & Furberg, *supra* note 3, at 1754.

42. Yasser M. Alatawi & Richard A. Hansen, *Empirical Estimation of Under-Reporting in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS)*, 16 EXPERT OPINION ON DRUG SAFETY 761 (2017); James R. Ward & P. John Clarkson, *An Analysis of Medical Device-Related Errors: Prevalence and Possible Solutions*, 28 J. MED. ENG'G & TECH. 2, 5 (2004) (describing underreporting rates for device-related medical errors ranging from 10 to 80%); see also *A Delicate Balance: FDA and the Reform of the Medical Device Approval Process: Hearing Before the S. Comm. On Aging*, 112th Cong. 11 (2011) (statement of Frederic S. Resnic, <http://www.aging.senate.gov/imo/media/doc/4132011.pdf> [<https://perma.cc/N3WU-LUUL>] (citing GAO estimate that only 0.5% of medical device adverse events are reported to the FDA).

43. Aaron V. Kaplan et al., *Medical Device Development: From Prototype to Regulatory Approval*, 109 CIRCULATION 3068, 3072 (2004) (“[T]he demonstration of safety and efficacy for a new medical device is a long, arduous, and expensive developmental path.”); Sharkey, *States Versus FDA*, *supra* note 10, at 1610–11; see also David Steinberg, Geoffrey Horwitz & Daphne Zohar, *Building a Business Model in Digital Medicine*, 33 NATURE BIOTECHNOLOGY 910, 914 (2015) (noting that the premarket studies required to bring a new high-risk device to market can cost nearly \$100 million).

44. Califf, *supra* note 35, at 693.

beneficial products from the market.⁴⁵ Thus, ensuring safety must be balanced against the dangers posed by overly-stringent regulation.

Central to striking this critical balance is understanding product risk. This Part describes the regulatory regimes—focusing on the FDA’s pre-market authorities and state tort and products liability actions—that apply to prescription drugs, medical devices, and biological products. Section I.A sets out the statutes and regulations that make up the federal regulatory regime. Section I.B describes the states’ tort and products liability laws, and the roles they play in regulating drugs and devices. Section I.C then characterizes the federal and state roles as two layers of a single regulatory system structured by certain twentieth century conceptions of medical product risk. Under this account, manufacturers’ obligations to produce and disseminate information are calibrated to the information deficits concerning product risk which exist for each product category and to the burdens imposed by regulation. In addition to being descriptive, this account provides the normative position from which the remainder of the Article will proceed. Section I.D then examines the Supreme Court’s pivotal role in creating this regulatory system.

A. Federal Regulation of Prescription Drugs and Medical Devices

The FDA sorts, or “classifies,” each medical product submitted for approval according to the statutory definitions of “drugs,” “devices,” and “biological products” contained in the federal Food, Drug, and Cosmetic Act (FDCA).⁴⁶ The FDA then assigns each product to the FDA center responsible for regulating the products in the relevant statutorily defined class.⁴⁷ The assigned center regulates the product under the appropriate statutory authorities. Under this system, a product’s statutory definition determines on a categorical basis the quantity and quality of information a manufacturer must provide to gain approval to market the product in the United States.

45. *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 227–28 (2011) (noting the impact of product liability suits on the availability of childhood vaccines).

46. 21 U.S.C. §§ 301–399i (2012). Biological products are defined in the Public Health Services Act, 42 U.S.C. § 262(i)(1) (2012) (“The term ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”).

47. The FDA is divided into sub-Agency level centers. Drugs are assigned to the Center for Drug Evaluation and Research (CDER) and devices to the Center for Devices and Radiologic Health (CDRH).

The FDA has significant latitude to classify a product as a drug or a device. The Agency may find that a product satisfies the statutory definition of “drug” under a number of provisions of 21 U.S.C. § 321.⁴⁸ The most relevant definition establishes that drugs are “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.”⁴⁹ This definition is sufficiently broad that “[c]onceptually, all FDA-regulated medical products meet the definition of ‘drug.’”⁵⁰ Out of this set of products, the FDCA defines a subset that also satisfy the definition of “devices.”⁵¹ Devices are described in terms that suggest a mechanical function: “instrument[s], apparatus[es], implement[s], machine[s], contrivance[s], implant[s].”⁵² A product that meets one or more of these descriptions is defined as a device if it “does not achieve its primary intended purposes through chemical action within or on the body of man.”⁵³ Thus, the FDA may classify a product as a device even if it achieves some of its effects through chemical means, as where those effects are not intended (for instance, are side effects) or where the chemical action takes place apart from the body (as occurs in many diagnostic tests).⁵⁴ On the other hand, the FDA may classify a

48. 21 U.S.C. § 321(g)(1) (2012). The full text of the definition provides that “drugs” are:

(A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Id.

49. *Id.*

50. FDA, FINAL GUIDANCE, CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES: GUIDANCE FOR INDUSTRY AND FDA STAFF (2017), <https://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm> [<https://perma.cc/N67F-B7G4>].

51. 21 U.S.C. § 321(h). The full text of the definition provides that a “device” is:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—(1) recognized in the official National Formulary, or the United States Pharmacopœia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Id.

52. *Id.* “[I]n vitro reagent” is the one descriptor that does not suggest a mechanical function. *Id.*

53. 21 U.S.C. § 321(h)(3).

54. See FDA, *supra* note 50, at 7–8.

mechanical product as a drug if the product achieves its intended purposes even in part through chemical action.⁵⁵

Once the FDA has determined that a product satisfies the statutory definition of a drug or device, the Agency assigns regulatory responsibility to either the Center for Drug Evaluation and Research (CDER) or the Center for Devices and Radiologic Health (CDRH), respectively. This assignment determines the set of statutory authorities to which a product is subjected. A manufacturer seeking approval to market a “new drug”⁵⁶ must submit a New Drug Application (NDA),⁵⁷ which imposes the most rigorous information-generating and disclosure requirements to which any FDA-regulated product is subjected.⁵⁸ Manufacturers must typically generate extensive amounts of new information about risk by conducting scientific studies, including at least two well-designed, Phase 3 clinical trials,⁵⁹ which “are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug”⁶⁰ These trials involve several thousand subjects and typically require several years to complete.⁶¹ Phase 3 trials are scientifically rigorous, employing the randomized assignment of subjects to active treatment and control arms, double-blinding (of subjects and investigators), pre-specification of endpoints, and detailed statistical analyses.⁶² Manufacturers must also

55. *Id.* Historically, the FDA has attempted to define some devices as drugs in order to bring those devices within the Agency’s drug regulatory authority. *See, e.g.,* AMP Inc. v. Gardner, 389 F.2d 825 (2d Cir. 1968) (FDA defining nylon ligature as a drug); *United States v. 48 Dozen Packages, More or Less, of Gauze Bandage Labeled in Part Sterilized*, 94 F.2d 641 (2d Cir. 1938) (discussing the FDA’s definition of gauze bandages as drugs).

56. “New drugs” are defined as drugs which are “not generally recognized, among experts . . . as safe and effective for use under the conditions prescribed, recommended,” or which “[have] not . . . been used to a material extent or for a material time under such conditions.” 21 U.S.C. § 321(p).

57. 21 U.S.C. § 355(b).

58. Jordan Paradise, *Reassessing Safety for Nanotechnology Combination Products: What Do Biosimilars Add to Regulatory Challenges for the FDA?*, 56 ST. LOUIS U. L. REV. 465, 479 (2012).

59. 21 C.F.R. § 312.21(c) (2019); *see also* FDA, DEVELOPMENT & APPROVAL PROCESS (DRUGS) (2018), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm> [<https://perma.cc/D5BC-FJAE>]. Before conducting Phase 3 trials, a manufacturer must present basic data and conduct Phase 1 and 2 clinical trials. *Id.* Phase one trials involve twenty to eighty healthy individuals to determine the metabolism and actions of the drug, its side effects, and early evidence on effectiveness. 21 C.F.R. § 312.21(a) (2019). Phase 2 trials include up to several hundred patients with the disease or condition for which the drug is to be marketed, in order “to evaluate the effectiveness . . . and to determine the common short-term side effects and risks.” 21 C.F.R. § 312.21(b).

60. 21 C.F.R. § 312.21(c); FDA, THE DRUG DEVELOPMENT PROCESS, STEP 3: CLINICAL RESEARCH (2016), <http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm> [<https://perma.cc/TE75-XGR4>].

61. 21 C.F.R. § 312.21(c).

62. Sanket S. Dhruva, Lisa A. Bero & Rita F. Redberg, *Strength of Study Evidence Examined by*

disclose extensive amounts of information that already exists.⁶³

In contrast to the NDA process for new drugs, the Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”)⁶⁴ established a relatively quick, low-cost process (the “Abbreviated New Drug Application,” or ANDA) for generic drugs.⁶⁵ Because generic drugs are copies of NDA-approved new drugs for which extensive safety and effectiveness information has already been generated and disclosed, an ANDA requires manufacturers to conduct only a small-scale study to prove “bioequivalence”—that the generic drug becomes available at the site of action in the body at the same rate and to the same extent as that of the brand drug.⁶⁶ No new safety information is required.⁶⁷

The Medical Device Amendments (MDA) to the FDCA⁶⁸ create a very different premarket evaluation regime for devices. The MDA establishes a three-tiered regulatory scheme, dividing devices into “Classes” depending on the level of risk they present.⁶⁹ No premarket assessment is required for the lowest-risk (Class I) devices.⁷⁰ Manufacturers who seek to market intermediate-risk (some Class I and most Class II) devices must submit a Section 510(k) “premarket notification,” including information establishing that the device is “substantially equivalent” to a device already on the market.⁷¹ In general, Section 510(k) submissions do not require clinical trials

the FDA in Premarket Approval of Cardiovascular Devices, 302 J. AM. MED. ASS’N 2679, 2684 (2009); Jonas Z. Hines et al., *Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review*, 7 PLOS MED. 1, 6 (2010); Daniel B. Kramer et al., *Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Clinical Studies Submitted to the Food and Drug Administration 2000–2007*, 17 AM. J. THERAPEUTICS 2, 4–6 (2010).

63. See, e.g., 21 C.F.R. § 314.50(d)(5)(vi) (2019) (requiring disclosure of animal data and information about related drugs).

64. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355(j) (2012)).

65. *Id.*

66. Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 J.L. MED. & ETHICS 598, 601 n.28 (2009). The Hatch-Waxman Act imposes on generic drug makers a “duty of sameness” regarding bioequivalence, the active ingredient(s), and the product label. 21 U.S.C. §§ 355(j)(2)(A)(ii), (v).

67. Emily M. Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245, 262 (2012).

68. Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified at 21 U.S.C. § 360 *et seq.*).

69. 21 U.S.C. § 360c(a) (establishing classification scheme for devices).

70. FDA, *Classify Your Medical Device: Class I/III Exemptions* (2016), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051549.htm> [<https://perma.cc/MQN3-2DTW>]. Manufacturers must comply with post-marketing requirements, including registration, labeling, and Good Manufacturing Practices. *Id.*

71. 21 C.F.R. § 807.87(f) (2019). The term “510(k)” comes from the section of the Food, Drug and Cosmetics Act that created the premarket notification process, which is now codified at 21 U.S.C.

that demonstrate safety. Manufacturers seeking to market the highest-risk (Class III) devices must submit a lengthy and detailed “Premarket Approval” (PMA) application, which, like the NDA process, requires manufacturers to produce and disseminate information about risk.⁷² The disclosure requirements are similar to those for a new drug undergoing the NDA process.⁷³

Although courts and others typically emphasize the rigorous nature of the PMA process,⁷⁴ the information-generating requirements are not as extensive as those imposed by the NDA process for new drugs. A PMA application may be supported by a single pivotal trial, as opposed to the multiple Phase 3 clinical trials typically required for new drug approvals.⁷⁵ Nearly two-thirds of original PMA approvals for cardiovascular devices have been granted on the basis of a single “pivotal” study.⁷⁶ Medical device regulation must employ the “least burdensome approach,” minimizing the amount of information required to provide a reasonable assurance of safety.⁷⁷ And the recently-enacted 21st Century Cures Act⁷⁸ requires the FDA to consider shifting the manufacturer’s information-generating obligations to the post-market phase when possible.⁷⁹

The information-generating requirements for high-risk device approval are further reduced by FDA practice. Several groups of academic medical researchers have pointed to weaknesses in the design of the pivotal trials the FDA accepted, including a lack of randomization in 73% and a lack of blinding in 86% of trials.⁸⁰ In the views of the authors, many studies were poorly designed and did not adequately control for the relevant variables.⁸¹ And many were flawed in other ways—they were of short duration, did not clearly define safety and effectiveness end points, failed

§ 360(k) (2012).

72. 21 U.S.C. § 360c(a).

73. *Id.* (requiring disclosure of known risk information, device composition, and manufacturing controls).

74. *See, e.g.,* Riegel v. Medtronic, Inc., 552 U.S. 312, 317 (2008) (“Premarket approval is a ‘rigorous’ process.” (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 477 (1996))).

75. 21 U.S.C. § 360c(a)(3)(D)(ii) (requiring “one or more well-controlled investigations”).

76. Dhruva, Bero & Redberg, *supra* note 62, at 2684.

77. 21 U.S.C. § 360c(f)(6)(C)(i)(II).

78. Pub. L. No. 114-255. 130 Stat. 1033 (2016).

79. 21 U.S.C. § 360e(c)(5)(C).

80. Dhruva, Bero & Redberg, *supra* note 62, at 2683 (noting that the majority of PMAs for cardiovascular devices were neither blinded nor randomized); Hines et al., *supra* note 62, at 2; Kramer et al., *supra* note 62, at 5 (noting that 40% of PMAs studied had employed randomization); Vinay K. Rathi et al., *Characteristics of Clinical Studies Conducted Over the Total Product Life Cycle of High-Risk Therapeutic Medical Devices Receiving FDA Premarket Approval in 2010 and 2011*, 314 JAMA 604, 607–08 (2015).

81. Kramer et al., *supra* note 62, at 4.

to collect complete data on important patient comorbidities, contained discrepancies in the numbers of patients enrolled and reported, and used “post hoc” data analyses.⁸² These flaws led one group to conclude that premarket approval “by the FDA is often based on studies that . . . may be prone to bias.”⁸³

Practical and ethical concerns limit the FDA’s ability to eliminate the information deficits related to medical device risk. Conducting randomized, double-blinded studies involving invasive procedures such as device implantation is generally considered unethical.⁸⁴ And medical devices are used in fewer patients than are drugs, making large device studies impractical. Nonetheless, it is clear that both by statute and in the FDA’s practice the information requirements for high-risk medical devices are not as robust as the requirements for new drugs.

Compared with the PMA process for high-risk devices, the Section 510(k) notification process for intermediate-risk devices imposes less stringent information disclosure requirements and no general requirement to generate new risk information. The manufacturer must disclose information that establishes the device is “substantially equivalent” to one already on the market (the “predicate device”).⁸⁵ Except in rare circumstances, the manufacturer is not required to generate new information about risk through clinical trials.⁸⁶ Because neither the manufacturer of the new device nor the manufacturer of its predicate device are required to submit new information about risk, courts have recognized that “devices that enter the market through § 510(k) have ‘never been formally reviewed under the MDA for safety or efficacy.’”⁸⁷

82. Dhruva, Bero & Redberg, *supra* note 62, at 2683–84.

83. *Id.* at 2679.

84. *Id.* at 2683. *But see* Rasha Al-Lamee et al., *Percutaneous Coronary Intervention in Stable Angina (ORBITA): A Double-Blind, Randomised Controlled Trial*, 391 LANCET 31 (2018) (reporting a multicenter U.K. study in which the control group was subjected to invasive sham coronary stenting procedures); Karolina Wartolowska et al., *Use of Placebo Controls in the Evaluation of Surgery: Systematic Review*, 348 BMJ g3253 (2014) (arguing that systematic review of fifty-three studies subjecting control subjects to sham surgery demonstrated minimal risk to subjects and significant benefit to medical knowledge base).

85. 21 U.S.C. § 360c(f)(1)(A)(ii) (2012). The FDCA defines a substantially equivalent device as one that has the same intended uses as its predicate, and that has either the same technological characteristics as its predicate or that “has different technological characteristics” and is shown to be “as safe and effective” and does not raise new safety concerns. 21 U.S.C. § 360c(i)(1)(A).

86. FDA, GUIDANCE FOR INDUSTRY & FDA: SAFETY AND PERFORMANCE BASED PATHWAY 6 (2019), <https://www.fed.gov/media/11269/download> [<https://perma.cc/5PD6-SMBF>] (describing preference to evaluate intermediate risk devices based on non-clinical trial evidence).

87. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 323 (2008) (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 493 (1996)).

As this review of federal premarket evaluation demonstrates, medical products enter the U.S. market with different quanta of information about risk, depending on the product category to which they belong. New drugs enter the market through the NDA process, which produces the most extensive quantum of risk information. Generic drugs enter the market with a more extensive quantum of risk information than new drugs, even though the ANDA process does not require new clinical data on risk. The information about generic drug risk includes the information generated by the manufacturer of NDA-approved drug of which the generic drug is a copy. In addition, by the time a generic drug enters the market, very large numbers of people will likely have been exposed to it for a long period of time, providing additional risk information. High-risk devices enter the market after PMA approval, which results in the production of a less extensive quantum of information than that produced by the NDA process. Intermediate-risk devices enter the market through Section 510(k) notification with the smallest quantum of risk information.

B. The States' Roles in Regulating Drugs and Devices: Common Law and Preemption Jurisprudence

The states provide the other important input to medical products regulation.⁸⁸ As a feature of their sovereignty, “[t]he States’ core police powers have always included authority . . . to protect the health, safety, and welfare of their citizens.”⁸⁹ Accordingly, states can regulate product safety through legislative and administrative means.⁹⁰ States also regulate product safety by providing common law remedies to injured consumers through tort and products liability law actions.⁹¹ Most relevant here, state products liability law provides for “failure-to-warn” actions, where the “foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of reasonable instructions or warnings.”⁹² Although courts and commentators often focus on the role these actions play in providing injured consumers the possibility of compensation⁹³ and incentivizing manufacturers to produce safer products and provide

88. Sharkey, *States Versus FDA*, *supra* note 10, at 1611.

89. *Gonzales v. Raich*, 545 U.S. 1, 42 (2005) (O’Connor, J., dissenting).

90. States, for example, regulate certain flame-retardant chemicals. *See, e.g.*, MINN. STAT. ANN. § 325F.071 (West 2015) (banning certain chemicals); CAL. VEH. CODE § 24016(a)(2) (West 2019) (requiring motor to automatically disengage in electric bicycles).

91. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 1 (Am. Law Inst. 1998).

92. *Id.* § 2(c).

93. *See, e.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 643 (2011) (Sotomayor, J., dissenting).

adequate warnings,⁹⁴ the focus here is on another role that failure-to-warn claims can play: these claims can incentivize or even force manufacturers to disclose risk information and to conduct additional research that generates new risk information.⁹⁵

But the states' legislative and administrative powers over medical products are limited: where state law overlaps with federal law, federal law may render state law inoperative.⁹⁶ Preemption doctrine provides the analytic framework through which courts manage these overlaps.⁹⁷ Congress can expressly preempt state laws.⁹⁸ Courts may find state laws to be impliedly preempted where Congress legislated in such a way as to indicate an intention to occupy the regulatory field,⁹⁹ where compliance with both the federal and state requirements is impossible,¹⁰⁰ or where state law stands as an obstacle to Congress's purposes and objectives.¹⁰¹ The MDA expressly preempts state regulation of medical devices through statutory or administrative premarket approval schemes.¹⁰² Lower courts have held that FDA approval of prescription drugs impliedly preempts state legislative or administrative attempts to ban sales of the drug.¹⁰³

Courts have also applied the federal preemption doctrine to limit the role of state tort and products liability law in regulating certain prescription drugs and medical devices. Because the FDCA does not contain an express preemption provision for prescription drugs,¹⁰⁴

94. *Id.* at 644.

95. Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 JAMA 308 (2007). *But see* Cahoy, *supra* note 27, at 625–26 (arguing that potential tort liability disincentivizes manufacturers from generating additional risk information).

96. The Supremacy Clause establishes that federal law is supreme when a state law conflicts with it. U.S. CONST. art. VI, cl. 2.

97. *See, e.g.*, Ernest A. Young, “*The Ordinary Diet of the Law*”: *The Presumption Against Preemption in the Roberts Court*, 2011 SUP. CT. REV. 253, 256 (2011).

98. *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 517 (1992).

99. *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 236 (1947).

100. *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142–43 (1963).

101. *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941). For a concise taxonomy and explanation of federal preemption doctrine, see *English v. General Elec. Co.*, 496 U.S. 72, 78–79 (1990).

102. 21 U.S.C. § 360k (2012); *see also* *Riegel v. Medtronic, Inc.*, 552 U.S. at 316 (noting that the MDA “swept back” state-level premarket approval systems for devices); *id.* at 340 (Ginsburg, J., dissenting) (noting that § 360k expressly preempts state premarket approval systems).

103. *Zogenix, Inc. v. Patrick*, No. CIV.A. 14-11689-RWZ, 2014 WL 1454696 (D. Mass. Apr. 15, 2014); *see also* Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 859 (2017) (“[F]ederal regulation is now generally characterized as dominant in this area.”); Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 430 (2015) (“[T]he conventional wisdom . . . is that states regulate medical *practice*, while the federal government regulates medical *products*.”).

104. *Wyeth v. Levine*, 555 U.S. 555 (2009). In fact, the Kefauver-Harris Amendments of 1962

preemption in the prescription drug context arises solely from the workings of implied conflict preemption. The Supreme Court has established that state tort and products liability verdicts against manufacturers create state requirements.¹⁰⁵ These requirements may conflict with FDA-imposed labeling requirements if compliance with both is impossible or if a state requirement would “stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.”¹⁰⁶ When compliance with both is impossible, courts’ preemption analyses of failure-to-warn claims have focused on whether the manufacturer is able to change the drug’s labeling without prior FDA approval to satisfy a jury-imposed requirement under state tort or products liability law.¹⁰⁷ In *Wyeth v. Levine*¹⁰⁸ the Supreme Court reasoned that the manufacturers of new (or, “brand”) drugs, whose products reach the market through the NDA process, may change the labeling through the FDA’s Changes Being Effected (CBE) regulation without the FDA’s prior approval.¹⁰⁹ Thus, compliance with state tort and product liability law and federal labeling requirement is not impossible.¹¹⁰ Further, the *Wyeth* Court held that state tort liability did not present an obstacle to the FDA’s mission of ensuring that prescription drugs are safe and effective.¹¹¹

By contrast, the Supreme Court has held that ANDA approval preempts failure to warn claims against generic drug manufacturers.¹¹² Generic drug manufacturers are not permitted to change the drug labeling except to maintain their label in conformity with the brand drug’s label.¹¹³ In both *PLIVA, Inc. v. Mensing*¹¹⁴ and *Mutual Pharmaceutical Co., Inc. v. Bartlett*,¹¹⁵ the Court found that this rendered generic manufacturers’

contained a savings clause limiting the preemptive effect to “direct and positive conflicts” between federal and state law. Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 793 (1962).

105. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324 (2008); *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 521 (1992).

106. *English*, 496 U.S. at 79 (quoting *Hines*, 312 U.S. at 67).

107. *Guilbeau v. Pfizer Inc.*, 880 F.3d 304, 308 (7th Cir. 2018) (“[The preemption analysis] turn[s] on whether a drug-maker may or may not change its label to add a warning without prior approval from the FDA.”).

108. 555 U.S. 555 (2009).

109. *Id.* at 568 (noting that the “changes being effected” regulation, 21 C.F.R. § 314.70(c) (2019), allows manufacturers to add or strengthen labeling language to ensure safety).

110. *Id.* at 573.

111. *Id.* at 581.

112. *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011).

113. *Id.* at 616.

114. 564 U.S. 604 (2011).

115. 570 U.S. 472 (2013).

compliance with differing state common law and FDA-imposed requirements impossible.¹¹⁶ In both cases the Court's majority only applied an impossibility analysis.

For medical devices, both express and implied preemption principles are relevant. The MDA includes an express preemption provision, 21 U.S.C. § 360k, establishing that:

[N]o State . . . may establish or continue in effect with respect to a device . . . any requirement . . . which is different from, or in addition to, any requirement applicable under this chapter to the device, and . . . which relates to the safety or effectiveness of the device¹¹⁷

In *Riegel v. Medtronic, Inc.*,¹¹⁸ the Court held that PMA approval of a high-risk device results in device-specific requirements for design, manufacturing, and labeling with which the manufacturer must comply, thus triggering section 360k.¹¹⁹ Any state failure-to-warn or design defect action that led to a damages award would create a state-imposed requirement different from or in addition to the requirements established by the FDA through the PMA approval process. Under *Riegel*, these state law actions are thus expressly barred by section 360k.¹²⁰

By contrast, for intermediate-risk devices marketed through the Section 510(k) notification pathway, design defect and failure-to-warn claims may escape express preemption. Premarket Section 510(k) review focuses on whether a new device is substantially equivalent to an already-approved intermediate-risk device.¹²¹ In *Medtronic, Inc. v. Lohr*,¹²² the Supreme Court held that Section 510(k) evaluation does “not ‘require’ [a cleared device] to take any particular form for any particular reason.”¹²³ Because Section 510(k) clearance does not impose device-specific requirements, the MDA's express preemption provision is not triggered.¹²⁴

116. *Id.* at 614–15; *Bartlett*, 570 U.S. at 476. The Court granted *Auer* deference to the FDA's interpretation of its own regulation, that the CBE was not available to generic manufacturers. *Id.* (citing *Auer v. Robbins*, 519 U.S. 452 (1997)).

117. 21 U.S.C. § 360k (2012)

118. 522 U.S. 312 (2008).

119. *Riegel*, 522 U.S. at 323–24.

120. *Id.* at 330.

121. 21 U.S.C. § 360c(f)(1)(A)(ii); 21 C.F.R. § 807.87(f) (2019).

122. 518 U.S. 470 (1996).

123. *Lohr*, 518 U.S. at 493.

124. *But see* Ralph F. Hall & Michelle Mercer, *Rethinking Lohr: Does “SE” Mean Safe and Effective, Substantially Equivalent, or Both?*, 13 MINN. J.L. SCI. & TECH. 737, 739 (2012) (arguing that the precedential value of *Lohr* has become “highly questionable”).

But even where claims against device manufacturers survive express preemption, they may be barred by implied preemption. In *Buckman Co. v. Plaintiffs' Legal Committee*,¹²⁵ the Supreme Court held that suits alleging fraud on the FDA stood as an obstacle to the Agency's ability to achieve the "delicate balance of statutory objectives" which Congress mandated.¹²⁶ *Buckman* potentially subjected all state law claims to preemption under an obstacle preemption theory. However, the *Riegel* Court later held that "parallel claims" may survive preemption analysis.¹²⁷ State law claims must fit through a "narrow gap," avoiding preemption only if they do not seek to impose requirements that are "different from, or in addition to" federal requirements, and only if they do not seek merely to enforce federal requirements.¹²⁸ The result is that in some circuits most suits against the manufacturers of PMA-approved devices are barred either by express or by implied preemption, while in other circuits many failure-to-warn claims will fit through the statutory gap.¹²⁹

These distinct frameworks result in different roles for state tort and product liability law. The role of state failure-to-warn claims is practically non-existent for PMA-approved devices and ANDA-approved generic drugs. Failure-to-warn claims play a somewhat uncertain role for Section 510(k)-cleared devices. And for NDA-approved brand drugs, failure-to-warn claims' role is relatively robust.

C. *An Information-Forcing Account of Medical Product Regulation*

Pre-market evaluation by the FDA and post-market failure-to-warn claims under state tort and products liability law are often described as separate, inherently conflicting regulatory systems.¹³⁰ Federal regulation

125. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001).

126. *Id.* at 341.

127. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 330 (2008) ("[Section] 360k does not prevent a State from providing a damages remedy for claims premised on a violation of FDA regulations; the state duties in such a case 'parallel,' rather than add to, federal requirements.")

128. *Riley v. Cordis Corp.*, 625 F. Supp. 2d 769, 776–77 (D. Minn. 2009); Jean M. Eggen, *Navigating Between Scylla and Charybdis: Preemption of Medical Device "Parallel Claims,"* 9 J. HEALTH & BIOMEDICAL L., 159, 161 (2013).

129. See George Horvath, Comment, *Recovery and Preemption: The Collision of the Medicare Secondary Payer Act and the Medical Device Amendments*, 103 CALIF. L. REV. 1353, 1379 n.184 (2015) (listing cases on both sides of the circuit split).

130. Richard A. Epstein, *What Tort Theory Tells Us About Federal Preemption: The Tragic Saga of Wyeth v. Levine*, 65 N.Y.U. ANN. SURV. AM. L. 485, 488 (2010) (arguing for field preemption of state tort and products liability law in medical products context); Lars Noah, *State Affronts to Federal Primary in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1 (2016) (arguing that federal regulation preempts state statutory and administrative regulation of prescription drugs).

may preempt state law, leaving injured patients with no recourse and limited means of obtaining compensation.¹³¹ State law may impose requirements that directly conflict with federal requirements.¹³² And state law may stand as an obstacle to the objectives of federal regulation, particularly the goal of fostering innovation and access through the creation of a single, nationwide regulatory regime.¹³³

Another description of state tort and products liability actions is that they serve as complements to federal regulation of drug and devices, filling in gaps left by the FDCA or created by the FDA's lack of resources or attention.¹³⁴ This section goes further, arguing that federal regulation and state failure-to-warn actions function as single emergent system that ensures the production and dissemination of a sufficient quantum of information about medical product risk to allow regulators, prescribers, and patients to determine that a product has a reasonable assurance of safety. This functional account is both descriptive and normative. As a descriptive account, it provides a better explanation for the Supreme Court's preemption holdings in the drug and device cases than other explanations. And as a normative matter, it is consistent with the important goal of ensuring safety, which federal and state regulation share.

In this account, the medical products regulatory system utilizes three sources of information about drug and device risk: (1) information that can be obtained simply by categorizing a product as a drug or device; (2) information generated before and during the FDA's premarket evaluation processes; and (3) information generated or disclosed through discovery and trial in failure-to-warn cases. The first of these reflects a twentieth-century understanding of medical products: that the ability to predict risk depends on whether a product is discovered or designed. In the mid-twentieth century, when the federal drug regulatory regime and state common law systems were expanding, most drugs were relatively small molecules, which had been "discovered" in nature.¹³⁵ In the years just prior to the original FCDA, Gerhard Domagk had discovered the precursor to the antibiotic sulfanilamide in a red dye, and Sir Alexander

131. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 643 (2011) (Sotomayor, J., dissenting) (discussing how preemption "strips generic-drug consumers of compensation when they are injured by inadequate warnings"); *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 333 (2008) (Ginsburg, J., dissenting) (discussing how preemption "effect[s] a radical curtailment of state common-law suits seeking compensation").

132. See *PLIVA*, 564 U.S. at 617–18 (majority opinion).

133. See *Riegel*, 552 U.S. at 326 (majority opinion) (noting the likely effects on innovation "if juries were allowed to apply the tort law of 50 States to all innovations").

134. See Cahoy, *supra* note 27, at 629; Kessler & Vladeck, *supra* note 13, at 463; Laakman, *supra* note 27, at 138–41.

135. *Looking Back*, *supra* note 17.

Fleming had isolated penicillin from a moldy petri dish.¹³⁶ At that time, the limited understanding of drug structure and function of human biochemistry made it nearly impossible to predict the existence of specific risks and to estimate the magnitude of those risks. Drug risks could be adequately characterized only by exposing large numbers of humans under controlled conditions.

By contrast, the mid-twentieth century model of medical device development was one of product “design.”¹³⁷ Because devices are designed, the site, mechanism, and nature of their actions—and hence their risks—were viewed as predictable. Thus, when Congress enacted the Medical Device Amendments in 1976, it created a tiered pre-market evaluation system in which the FDA sorts devices into high, intermediate, and low risk categories based on information about device function, composition, design, and intended use, all of which are available before any human exposure.¹³⁸

Under these twentieth-century views, a large information deficit exists regarding the risks posed by all new drugs, while a much smaller information deficit exists for new medical devices. The remaining two sources of information are used in a calibrated fashion to overcome these information deficits. For new drugs, the regulatory system uses a two-layered approach that ensures maximal information production and dissemination.¹³⁹ The first layer of regulation is the federal pre-market NDA process. But even Phase 3 clinical trials cannot identify all significant new drug risks, and thus, new drugs enter the market with many unknown risks. State tort and products liability law serve as a second layer of regulation that forces the production and dissemination of risk information as very large numbers of people are exposed to a new drug.

For generic drugs, the regulatory system uses a single layered approach that requires the production of far less information about risk.¹⁴⁰ But

136. *Id.*

137. See, e.g., Fred B. Hovey, *Therapeutic Devices Under the Federal Food, Drug, and Cosmetic Act*, 3 FOOD DRUG COSM. L.Q. 97, 97 (1948) (“The properties of drugs . . . are not obvious on ocular inspection . . . but the properties of most . . . therapeutic devices are obvious, and the need for . . . warnings regarding their uses and dangers is not apparent.”).

138. See, e.g., 21 C.F.R. § 888.3310 (2019) (classifying hip prostheses as a Class II device based on function (“prevents [hip] dislocation in more than one anatomic plane”), composition (“femoral component made of alloys, such as cobalt-chromium-molybdenum”), and intended use (“to replace a hip joint”)).

139. See *Wyeth v. Levine*, 555 U.S. 555, 579 (2009) (noting FDA’s earlier position that state law provides an additional layer of protection against drug risks); Sharkey, *States Versus FDA*, *supra* note 10, at 1613–14.

140. See Pub. L. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355(j) (2012)); Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA*

generic drugs arrive at the FDA for evaluation with an extensive quantum of risk information. First, there is the information generated by the manufacturer of the NDA-approved drug of which the generic drug is a copy. Further, by the time a generic drug enters the market, very large numbers of people will likely have been exposed to the brand version for a long period of time, providing additional risk information that mitigates the deficits with which new drug entered the market. Post-market failure-to-warn liability would in theory provide little added risk information.

For medical devices, the information deficits are smaller at the outset. Device risk can be sorted into categories based on knowledge of device function, composition, design, and intended use, all of which are available before any human exposure.¹⁴¹ The rationale for human studies arises less from the need to identify and quantify unforeseeable risks and more from the need to verify that known risks have been adequately addressed by the manufacturer's design and labeling choices. The smaller information deficits (relative to the information deficit for new drugs) about high-risk device risk can be addressed using a less extensive and less rigorous pre-market evaluation process. Once this evaluation has been completed, state failure-to-warn actions would in theory provide little additional risk information relative to the burdens that allowing such actions would impose.

For intermediate risk (Class II) devices, the regulatory system also uses a singled-layered approach to information production.¹⁴² Federal regulation through the Section 510(k) clearance process does not require the generation of new risk information. This leaves a small information deficit that state tort and products liability law can, in some cases, mitigate.

The overall system of regulation, including federal and state regulation of drugs and devices, thus functions as a mechanism that imposes a calibrated set of obligations on manufacturers to generate and disclose information about product risk.¹⁴³ Before proceeding, three important qualifications to this account must be addressed. The first qualification is that the account is intended as a functional description; it is not intended to imply that the system was designed solely or even primarily to ensure that information production and dissemination match the information needed to ensure product safety. Although ensuring safety has been a primary goal, calibrating information requirements across new drugs, generic drugs, high risk devices, and intermediate risk devices was not at the top of any decision-maker's priorities.

and Implications for Nanobiotechnology, 37 J.L. MED. & ETHICS 598, 601 & n.28 (2009).

141. See *supra* note 138 and accompanying text.

142. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 477 (1996).

143. See Cahoy, *supra* note 27, at 629; Laakman, *supra* note 27, at 138.

Many other policy considerations have informed the individual choices by Congress, the FDA, and the courts. Information production was key to Congress's creation of the FDA pre-market evaluation processes, but the structure of these processes balanced many competing policy goals. Congress permitted intermediate-risk device manufacturers to market their devices with the minimal information required by Section 510(k) notification so that existing devices did not have to be withdrawn from the market pending PMA evaluation and to avoid conferring an unfair competitive advantage on manufacturers with devices already on the market.¹⁴⁴ State courts expanded the reach of their tort and products liability laws between the 1950s and 1970s based on principles such as deterrence, cost spreading, and "reduc[ing] the hazards to life and health in defective products."¹⁴⁵ The U.S. Supreme Court, in finding that FDA approval of generic drugs preempts state law failure-to-warn claims, recognized Congress's policy goal of lowering prescription drug prices.¹⁴⁶ And in finding that FDA approval of high-risk medical devices through the PMA process preempts state law claims, the Court recognized that nationally uniform regulation would promote the development of new device technologies.¹⁴⁷ This Article's claim, therefore, is not that federal and state regulation of drugs and devices can be described as a system designed ab initio, but rather as an emergent, functional system of calibrated information-forcing obligations.

The second qualification recognizes the asymmetries between the information-forcing capabilities of the FDA premarket evaluation processes and state tort and product liability law. The federal NDA process, the PMA process, and (through incorporation of information generated by the reference brand drug) the ANDA process all result in the reliable production of risk information. The one exception is the Section 510(k) notification process, which results in little to no information about risk. By contrast, the quantity and quality of information produced by tort and product liability law is much less certain.

Anecdotal claims for the information-forcing function of tort and product liability law abound. Tort and products liability actions have been credited with forcing information about previously undisclosed product

144. Catherine M. Sharkey, *Products Liability Preemption: An Institutional Approach*, 76 GEO. WASH. L. REV. 449, 486 n.172 (2008).

145. *Escola v. Coca Cola Bottling Co. of Fresno*, 150 P.2d 436, 440 (Cal. 1944) (Trainor, J., concurring).

146. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 612–13 (2011).

147. *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 326 (2008); see *infra* notes 160–178 and accompanying text.

risks into the public's awareness in contexts as varied as automotive defects,¹⁴⁸ handgun safety,¹⁴⁹ and prescription drugs.¹⁵⁰ But the utility of tort and products liability actions as information-forcing mechanisms is controversial in general and vulnerable to powerful criticisms in the drug and device context.¹⁵¹ In fact, many of the anecdotes crediting tort and product liability actions with forcing the disclosure of risk information for certain drugs break down on closer inspection.

Merck's withdrawal of its blockbuster anti-inflammatory pain reliever, Vioxx, is one of the most frequently cited success stories for information-forcing through tort and product liability law. Merck withdrew the drug on September 29, 2004, after the Data Safety Monitoring Board of an ongoing study found an increased risk of stroke and heart attack.¹⁵² By August, 2001, sufficient data had been published in the peer-reviewed medical literature to permit researchers at the Cleveland Clinic to conclude that use of COX-2 inhibitors, including Vioxx, increased the risk of myocardial infarction.¹⁵³ The earliest products liability cases were filed *after* this date.¹⁵⁴ Similarly, commentators have credited a lawsuit filed in August 2001 with forcing the manufacturer of the antidepressant drug Paxil to add warnings to the label cautioning that the drug could be habit forming.¹⁵⁵ The label change came three months after the suit was filed. However, clear evidence of a withdrawal-like syndrome on termination of treatment had been extensively presented in the medical literature by the mid-1990s.¹⁵⁶ In fact, the manufacturer's requests to change the Paxil

148. Nora F. Engstrom, *When Cars Crash: The Automobile's Tort Law Legacy*, 53 WAKE FOREST L. REV. 293, 328–32 (2018).

149. Wendy Wagner, *Stubborn Information Problems & the Regulatory Benefits of Gun Litigation*, in *SUING THE GUN INDUSTRY: A BATTLE AT THE CROSSROADS OF GUN CONTROL AND MASS TORTS* 271, 271 (Timothy D. Lytton ed., 2009).

150. Kesselheim & Avorn, *supra* note 95, at 309.

151. Timothy D. Lytton, *Introduction: An Overview of Lawsuits Against the Gun Industry*, in *SUING THE GUN INDUSTRY: A BATTLE AT THE CROSSROADS OF GUN CONTROL AND MASS TORTS* 1, 24 (Timothy D. Lytton ed., 2009); Peter H. Schuck, *Why Regulating Guns Through Litigation Won't Work*, in *SUING THE GUN INDUSTRY: A BATTLE AT THE CROSSROADS OF GUN CONTROL AND MASS TORTS* 1, 233 (Timothy D. Lytton ed., 2009).

152. FDA, *FDA Public Health Advisory: Safety of Vioxx* (2013), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm> [<http://perma.cc/5NBF-MQWM>].

153. *See generally* Debabrata Mukherjee, Steven E. Nissen & Eric J. Topol, *Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors*, 286 JAMA 954 (2001) (summarizing available clinical evidence of Vioxx risks).

154. *See, e.g.*, *Lauderdale v. Merck & Co.*, No. 1:01CV418D-B, 2002 WL 449423, at *1 (N.D. Miss. Feb. 4, 2002) (earliest locatable claim against Merck over cardiovascular risks of Vioxx).

155. Kesselheim & Avorn, *supra* note 95, at 310.

156. A PubMed search (using search terms "paroxetine" and "withdrawal") revealed numerous

label came in response to an FDA action letter sent in January 2000.¹⁵⁷ Again, the information about the drug's dangers was clearly available to the medical community and the FDA long before litigation reached the discovery phase.

But tort and product liability law are not devoid of information-forcing capabilities. Even in the cases just discussed, the actions may have brought the information that was already known about product risk into the awareness of a broader population and may have focused the FDA's and the manufacturers' attention on the risks. And beyond the specific information that may be forced in an individual case, state law actions may serve as a general incentive for manufacturers to disclose information about product risk.

The third qualification to note is that this account is incomplete in that it does not consider the full gamut of regulatory inputs that lead to information generation and disclosure. Drug and device manufacturers are obligated to report certain adverse events to the FDA, and the agency has the authority to require post-market clinical studies for some products.¹⁵⁸ Independent researchers may study drugs and devices even after their approval. Clinical experience accrues over time and is shared through formal and informal information networks.¹⁵⁹

Recognizing that the account of medical product regulation is descriptive, that it may somewhat overstate the efficacy of state common law actions to force information, and that it is incomplete, the next section turns to the Supreme Court's role in creating the medical product regulatory system.

D. The Supreme Court's Role in Creating the Medical Product Regulatory System

The Supreme Court has played a key role in determining the contours of this calibrated system by determining the role of state regulation through its preemption holdings. In contrast to other accounts of the Court's preemption holdings in the drug and device cases, the information-forcing account presented here provides a comprehensive

case studies, literature reviews, and expert opinions by 1996.

157. See Letter from Russel Katz, Dir., Div. of Neuropharmacological Drug Products, to Susan Weill, Assoc. Dir., U.S. Regulatory Affairs (2002), http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/20982ltr.pdf [<https://perma.cc/SZ42-JZHF>].

158. JOHNSON 2016, *supra* note 3, at 27.

159. Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanism for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 389–91 (2014).

explanation of the outcomes in *Lohr*, *Buckman*, *Riegel*, *Wyeth*, *PLIVA*, and *Mutual Pharmaceutical*. The Court itself has explained its preemption holdings as implementing statutes that embody Congress's policies relating to safety, cost-containment, the promotion of innovation through national regulatory uniformity, and competitive fairness.¹⁶⁰ But many of these considerations have been mentioned only to explain the holding for the case in which they are invoked, ignoring the fact that the same considerations are germane to other cases in which they would point to a different outcome. Concerns that tort and products liability verdicts may drive up costs support preempting tort and products liability claims against generic drug manufacturers, but these same concerns would also support preempting all claims against the manufacturers of Section 510(k) cleared devices, which are far more common than PMA-approved devices.¹⁶¹ A policy of promoting innovation by establishing a nationwide, uniform regulatory environment supports preempting claims against the manufacturers of high-risk, PMA-approved devices, but that policy would also support preempting claims against the developers of new drugs and intermediate-risk devices. Thus, none of these explanations can fully account for the complex, nuanced preemption landscape that currently exists in the medical products context.

A full discussion of scholars' efforts to understand the Court's preemption decisions is beyond the scope of this Article. But several general themes—often overlapping—emerge from this literature. One general theme focuses on *sub rosa* changes to preemption doctrine in which the Court is said to be in the process of implementing. Since the Court's 1947 decision in *Rice v. Santa Fe Elevator Corp.*,¹⁶² courts have at least nominally and at least in many cases applied a presumption against preemption.¹⁶³ But many scholars argue that the Supreme Court has tacitly inverted preemption doctrine, so that the Court now applies a presumption *in favor of* preemption.¹⁶⁴ And some have argued that the

160. *Id.*; *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 626 (2011); *Medtronic, Inc., v. Lohr*, 518 U.S. 470, 478 (1996).

161. JOHNSON 2016, *supra* note 3, at 4 (showing that 35% of devices were marketed through a Section 510(k) notification compared with 1% through PMA-approval).

162. 331 U.S. 218 (1947).

163. *Id.* at 230 (“[W]e start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.”).

164. *See, e.g.*, Erwin Chemerinsky, *Empowering States When it Matters: A Different Approach to Preemption*, 69 BROOK. L. REV. 1313, 1319 (2004) (“The only way to make sense of the [*Geier*] case is to see it as putting a presumption in favor of preemption.”); Mary J. Davis, *Unmasking the Presumption in Favor of Preemption*, 53 S. C. L. REV. 967, 1013 (2002) (arguing that the Court's “preemption rules lead[] to the application of an implicit presumption in favor of preemption”);

Court has implicitly abandoned its stated approach, in which it discretely analyzes express and implied preemption, and now conducts either “a veiled implied preemption analysis” in express preemption cases¹⁶⁵ or applies a “unitary standard, merging previously discrete analytical elements into a single process.”¹⁶⁶ The unitary standard argument holds that the Court’s preemption analysis is actually “a single integrated process containing multiple factors.”¹⁶⁷ Taken to an extreme, this argument sees a danger that each preemption decision becomes “an ad hoc federalism analysis open to over-reliance on policy judgments and broad judicial discretion.”¹⁶⁸

A second general theme focuses on the critical attitudes of some of the Justices toward tort and product liability law.¹⁶⁹ Commentators posit a variety of factors—an “onslaught . . . of reports about excessive tort liability and run-away jury verdicts”¹⁷⁰ in the 1990s, “value choices to limit civil rights laws and to protect business,”¹⁷¹ and concerns about non-uniform regulatory environments—that may have influenced some Justices. But whatever the origins, many believe that the Court has grown increasingly hostile to common law litigation in the consumer products context.

A third general theme postulates various agendas that at least some of the Justices seek to implement. Focusing on the products liability cases, Professor Catherine Sharkey notes that Chief Justice Roberts and Justices Alito, Scalia, and Thomas have sought to “rein in agencies’ authoritative power by curtailing [the *Chevron* and *Auer*] doctrines that accord deference to agency interpretations of statutes and regulations.”¹⁷² But in addition to hostility toward the administrative state, these same justices have also expressed hostility toward state tort and products liability law.¹⁷³ Sharkey argues that “the object of vilification is regulation itself, whether

Gillian E. Metzger, *Federalism and Federal Agency Reform*, 111 COLUM. L. REV. 1 (2011) (“*Watters v. Wachovia Bank* appeared to apply a presumption [in favor] of preemption.”).

165. See Davis, *supra* note 164, at 1004.

166. Jean M. Eggen, *The Mature Product Preemption Doctrine: The Unitary Standard and the Paradox of Consumer Protection*, 60 CASE W. RES. L. REV. 95, 97 (2009).

167. *Id.* at 134.

168. *Id.* at 144.

169. Davis, *supra* note 164, at 1009 (“[T]he Court’s distrust of products liability actions is greater than its interest in determining congressional intent or preserving traditional state authority.”).

170. *Id.* at 1017.

171. Chemerinsky, *supra* note 164, at 1315.

172. Catherine M. Sharkey, *The Administrative State and the Common Law: Regulatory Substitutes or Complements?*, 65 EMORY L.J. 1705, 1709 (2016).

173. *Id.* at 1708–09.

by agency or common law.”¹⁷⁴ Preemption is thus simply one piece of a larger anti-regulatory, pro-business agenda.

Professors Lee Epstein and William Landes, and Judge Richard Posner examined the pro-business explanation empirically.¹⁷⁵ Using a database of Supreme Court cases between 1946 and 2011 in which at least one party at oral argument was a business, they found that the Roberts Court more frequently granted certiorari in cases where a business lost in the lower court and reversed those lower court decisions more often than either the Burger or Rehnquist Courts had.¹⁷⁶ Further, when the business entity had won below, the Roberts Court affirmed more frequently than its predecessors had.¹⁷⁷ Looking at the level of individual Justices, they found that “five of the ten Justices who . . . have been the most favorable to business are currently serving.”¹⁷⁸

These broad analyses of the Supreme Court’s preemption jurisprudence provide possible explanations for the decisions in the drug and device cases. But their descriptive value for the overall system of regulation for medical products described in section I.C is limited. In particular, these accounts encounter difficulties explaining the residual role that is left to the states after the *Lohr*, *Buckman*, *Riegel*, *Wyeth*, *PLIVA*, and *Mutual Pharmaceutical* decisions. State failure-to-warn claims against the manufacturers of NDA-approved brand drugs will likely survive preemption defenses, as may failure-to-warn and design defect claims that can be plead as parallel claims against the manufacturers of intermediate risk, Section 510(k)-cleared devices in many circuits. Explanations based on a strong presumption in favor of preemption or on a widely held dissatisfaction with state tort and product liability actions face difficulties when applied to *Lohr* and *Wyeth*. Likewise, explanations based on a pro-business deregulatory agenda or the use of a tacit presumption in favor of preemption suggest that all state law claims against drug and device manufacturers should be preempted. Thus, none of these explanations can account for the complex,

174. Catherine M. Sharkey, *The Anti-Deference Pro-Preemption Paradox at the U.S. Supreme Court: The Business Community Weighs in*, 67 CASE W. RES. L. REV. 805, 806, 809 (2017) (listing other scholars who have argued that the Roberts Court’s decisions embody a pro-business, anti-regulatory agenda).

175. Lee Epstein, William M. Landes & Richard A. Posner, *How Business Fares in the Supreme Court*, 97 MINN. L. REV. 1431, 1471 (2013).

176. *Id.* at 1472.

177. *Id.*

178. *Id.* But see Michael S. Greve et al., *Preemption in the Rehnquist and Roberts Courts: An Empirical Analysis*, 23 SUP. CT. ECON. REV. 353, 385 (2015) (concluding based on empirical analysis that an explanation for the Roberts Court’s preemption case outcomes “must be sought in doctrine, rather than raw ideology”).

nanced preemption landscape that currently exists in the medical products context.

The information-forcing account set out here offers a description of medical products regulation by the FDA and state failure-to-warn actions that is more comprehensive than these other accounts. The information-forcing account considers all three sources of risk information to explain the application of federal and state regulatory inputs to new drugs, generic drugs, high-risk devices, and intermediate-risk devices. This information-forcing account also provides the normative position taken in this Article, which is that a regulatory system that calibrates manufacturers' obligations to produce and disseminate information about product risk to the existing information about risk is desirable as a policy matter.

II. THE REGULATORY GAP IN COMBINATION PRODUCTS REGULATION

A developing regulatory gap threatens to subvert the calibrated information-forcing mechanism described in section I.C. This gap allows certain new drugs to reach patients without undergoing the rigorous information-forcing premarket NDA evaluation (instead reaching the market through the PMA process) and without being subjected to information-forcing post-market state law actions. The regulatory gap is the result of a “new” type of medical product—combination products—especially those that consist of a new drug and a high-risk medical device.¹⁷⁹ Congress created the federal side of this gap in 1990.¹⁸⁰ The state side of the gap, however, has emerged only recently, through lower courts' preemption decisions. Part II.A provides an introduction to combination products and the risks they may present. Part II.B then uses an extensive line of cases involving the “Infuse Bone Graft/Lt-Cage Lumbar Tapered Fusion” combination product (“Infuse/LT-Cage product”) to illustrate the regulatory gap.

A. *Combination Products: A Primer*

FDA regulations define combination products as products composed of two or more of the traditional, non-combination product categories, “i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic,”

179. “Combination products” are defined as products that consist of more than one product type, that is, some combination of a drug and device, a biologic and a device, a drug and a biologic, or a drug and a device and a biologic. 21 U.S.C. § 353(g) (2012); 21 C.F.R. § 3.2(e) (2019).

180. *See infra* Part III.

which may be combined into a single entity, packaged together, or packaged separately but labeled for use with one-another.¹⁸¹ Regulating combination products poses difficult challenges for the FDA, given that regulating each of the constituents requires specialized expertise.¹⁸² This Article focuses on combination products that include a medical device, which raises the additional challenge of determining the appropriate role of state tort and product liability actions.¹⁸³ Section II.A.1 discusses how combination products form an increasingly large portion of all products that are in use today, and will continue to grow in importance relative to the traditional, non-combination products over the foreseeable future. Section II.A.2 then explains why predicting the risks of a combination product is more difficult than for other products, including non-combination new drugs.

1. *The Range and Growth of the Combination Products Category*

The FDA has approved a wide array of drug-device combination products. These include:

- The Infuse/LT-Cage product. This product is used to fuse adjacent vertebrae in the spines of patients with low back pain due to degenerative disc disease.¹⁸⁴
- Drug eluting stents, which consist of a stent device—a metal mesh tube that physically holds open a narrowed artery—which is coated by a drug.¹⁸⁵
- Implantable, battery-powered pump devices, which can deliver drugs, such as insulin, on an ongoing basis or to specific regions in the body.¹⁸⁶
- Smart pills, which combine a drug and a miniaturized transmitter allowing patients and their physicians to monitor

181. 21 C.F.R. § 3.2(e).

182. *See, e.g.*, Foote & Berlin, *supra* note 4, at 620; Paradise et al., *supra* note 66, at 602.

183. Because most of the relevant biologics are regulated by the FDA's drug authorities, drugs and biologics are treated together in this Article.

184. FDA, SUMMARY OF SAFETY AND EFFECTIVENESS DATA: MEDTRONIC INFUSE, PMA NUMBER P000058 (2002), https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf [<https://perma.cc/F8QJ-DVAK>].

185. FDA, HIGHLIGHTS OF PRESCRIBING INFORMATION: ABILIFY MYCITE (2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207202lbl.pdf [<https://perma.cc/ZS48-7S4T>].

186. *See* FDA, PREMARKET APPROVAL, PMA P800036 (2018), <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P800036> [<https://perma.cc/RQL8-CS8H>]. The Infusaid Implantable Insulin Pump was first approved as a Class III medical device in 1982, before the legal definition of combination product existed. *Id.* The pump is currently classified as a combination product. *Id.*

compliance with a prescribed antipsychotic drug regimen.¹⁸⁷

- Transdermal patches, which deliver a drug at a consistent rate through the skin for hours or days.¹⁸⁸

Drug-device combinations form an important and growing part of the current-day medical treatment armamentarium. Premarket evaluation of these products now accounts for a significant portion of the FDA's time and effort.¹⁸⁹ Between 2000 and 2002, fewer than 1% of all PMA approvals were for combination products; in the two most recent years for which data is available, 16% of all PMA approvals have been for combination products.¹⁹⁰ Combination products submitted for approval through the FDA's drug and biological product pathways demonstrate a similar pattern, with steady increases between 2012 and 2015.¹⁹¹

Many observers have suggested that combination products will soon be the largest category of products submitted to the FDA.¹⁹² Industry analysts estimate that as many as one-third of all products in development are combination products.¹⁹³ These products include more sophisticated smart

187. Yieyie Yang, *The First FDA Approval of a Drug-device Combination Product that Tracks Patients' Ingestion of Medication*, FINNEGAN (Nov. 13, 2007), <https://www.finnegan.com/en/insights/blogs/ip-fda-blog/the-first-fda-approval-of-a-drug-device-combination-product-that-tracks-patients-ingestion-of-medication.html> [<https://perma.cc/Y36T-DEDT>] (explaining that the label describes the product as a drug-device combination product "comprised of aripiprazole tablets embedded with an Ingestible Event Marker (IEM)"); Letter from Mitchell V. Mathis, Dir., Div. of Psychiatry Products, to Michael Fahmy, Dir., Global Regulatory Affairs, (Nov. 13, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/207202Orig1s000ltr.pdf [<https://perma.cc/YC4X-5X22>]. Contact with gastric acid powers a transmitter whose signal is detected by a wearable monitor that links to a cell-phone. See Yang, *supra* note 182.

188. Michael N. Pastore et al., *Transdermal Patches: History, Development and Pharmacology*, 172 BRITISH J. PHARMACOLOGY 2179, 2180 (2015).

189. See FDA, FY 2016 PERFORMANCE REPORT TO CONGRESS FOR THE OFFICE OF COMBINATION PRODUCTS 13, <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/CombinationProducts/UCM606678.pdf> [<https://perma.cc/4UCE-DWJ8>] (documenting 357 new combination products approval submissions).

190. This is derived from data publicly available on the FDA PMA Approval website. I searched all FDA PMA approvals from the FDA website and constructed a spreadsheet that facilitated the calculation of the number of PMA approvals each year. See *Premarket Approval (PMA)*, FDA (May 16, 2019), <https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma> [<https://perma.cc/T623-9ZFN>]. I then repeated this process but limited the search to combination products. I then constructed a ratio of total PMA approvals to combination product approvals by CDRH each year. In 2016 CDRH granted a total of 2,563 PMA approvals, of which 414 (16.2%) were combination products; in 2017 the numbers were 2,718 and 422, respectively (15.5%). *Id.*

191. See FY 2016 PERFORMANCE REPORT, *supra* note 189, at 11. In 2015, the majority of combination products were submitted to CDER (53%), followed by CDRH (36%) and CBER (11%). *Id.*

192. See, e.g., SHAYNE C. GAD & SAMANTHA GAD-MCDONALD, BIOMATERIALS, MEDICAL DEVICES, AND COMBINATION PRODUCTS: BIOCOMPATIBILITY TESTING AND SAFETY ASSESSMENT 387, 388 tbl.17.1 (2015); Foote & Berlin, *supra* note 4, at 620–21; Mark Lavender, *Regulating Innovative Medicine: Fitting Square Pegs in Round Holes*, 1 DUKE L. & TECH. REV. 1, 4 (2005).

193. Drues, *supra* note 34.

pills, which will deliver a drug in a user-controlled manner;¹⁹⁴ anticancer drugs coated by a sphere of lipid molecules, which will permit higher doses to be administered to a tumor while limiting toxicity to the rest of the body¹⁹⁵; and cultured human cells mounted onto a physical matrix for implantation, which can restore damaged regions of the body.¹⁹⁶ The National Institutes of Health (NIH) is currently funding a variety of studies that could lead to the development of technologies that will be implemented as combination products.¹⁹⁷

This shift toward the development of combination products by the medical products industry will likely be accompanied by a shift toward the use of such products by health care providers. Combination products may be more effective than non-combination products.¹⁹⁸ And combination products may reduce certain risks posed by non-combination products.¹⁹⁹ As the shift to combination product development and use progresses, increasing numbers of patients will be exposed to combination products. With this increase, more injuries related to combination products will occur, and the portion of injuries arising from combination products will rise relative to injuries arising from non-combination products.

2. *Synergistic Risks of Combination Products: Challenging the Scientific Capacity to Predict Risk*

Every drug-device combination product poses a spectrum of risks, only some of which are foreseeable. The ability to predict the risks of a combination product raises the same considerations that are relevant to the individual constituents. Specifically, the risks posed by a new drug incorporated into a combination product may be as unforeseeable as the risks posed by the same new drug used by itself. Although some risks may be reduced, as where an active drug is encapsulated in a lipid coating or selectively delivered to a localized site, new-drug risks can neither be

194. See Matthew Avery & Dan Liu, *Bringing Smart Pills to Market: FDA Regulation of Ingestible Drug/Device Combination Products*, 66 FOOD & DRUG L.J. 329, 332–34 (2011).

195. Sophie Marchal et al., *Anticancer Drug Delivery: An Update on Clinically Applied Nanotherapeutics*, 75 DRUGS 1601, 1604 fig.1 (2015).

196. See Lichun Lu et al., *Tissue Engineered Constructs: Perspectives on Clinical Translation*, 43 ANNALS BIOMEDICAL ENGINEERING 796, 796 (2015); Catarina Medeira, *Advanced Cell Therapies for Articular Cartilage Regeneration*, 33 TRENDS BIOTECHNOLOGY. 35, 36 fig.1 (2015).

197. See *Delivery Systems and Devices for Drugs and Biologics*, NAT'L INST. BIOMEDICAL IMAGING & BIOENGINEERING, <https://www.nibib.nih.gov/research-funding/drug-and-gene-delivery-systems-and-devices> [<https://perma.cc/K5NV-48WG>] (listing sixty-five funded studies in the “Funded Projects” tab).

198. See *supra* notes 185–195 and accompanying text.

199. See *supra* note 195.

completely foreseen nor eliminated.²⁰⁰ Thus, drug-device combination products arrive for FDA premarket evaluation with very large deficits in information because of the presence of a new drug.

Further, combining a drug and a device may create risks that exceed the arithmetic sum of the risks of the individual products. These risks, referred to as “synergistic”²⁰¹ or “superadditive”²⁰² risks, are not unique to combination products. Drug-drug combinations²⁰³ may pose risks that are quantitatively greater than the risks of each drug alone. For example, the risk of central nervous system depression caused by a combination of an alcohol and a benzodiazepine (e.g., Valium) exceeds the additive risk of respiratory depression by each drug used by itself.²⁰⁴ These quantitative synergistic risks are well-known to clinicians and to regulators. Phase three clinical trials are designed in part to evaluate these risks.

Less commonly, drug-drug combinations may present risks which neither individual drug component presents. Neither the antidepressant drug Paxil nor the cholesterol-lowering drug Pravachol has been shown to raise blood glucose levels, but patients who use both are at an increased risk for elevated blood glucose levels,²⁰⁵ which can be devastating for those who are already treated for diabetes.²⁰⁶ These types of qualitative synergistic risks are more difficult to predict than quantitative synergistic risks. Even large, rigorous Phase 3 clinical trials have failed to identify some of these risks.²⁰⁷

Combination products present synergistic risks as well. Some of these risks are quantitative. Both an injection catheter and a drug carry the risk

200. Avery & Liu, *supra* note 194, at 331 (describing how controlled delivery of certain drugs can reduce their toxicity).

201. FDA, ISO 10993-1, GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 34 (2016), <https://www.fda.gov/media/85865/download> [<https://perma.cc/W3EN-D9VG>] (discussing appropriate testing to detect “synergistic mechanisms”).

202. Jennifer B. Treweek, Amanda J. Roberts & Kim D. Janda, *Superadditive Effects of Ethanol and Flunitrazepam: Implications of Using Immunopharmacotherapy as a Therapeutic*, 7 MOLECULAR PHARMACOLOGY 2056, 2058 (2010) (discussing the “superadditive effects” of ethanol and benzodiazepines on the central nervous system).

203. Drug-drug combinations do not satisfy the definition of a combination product, because the components are both from the same product category.

204. Treweek, Roberts & Janda, *supra* note 202, at 2058.

205. NP Tatonetti et al., *Detecting Drug Interactions from Adverse-Event Reports: Interaction Between Paroxetine and Pravastatin Increases Blood Glucose Levels*, 90 CLINICAL PHARMACOLOGY & THERAPEUTICS 133, 133 (July 2011).

206. See Feng Li et al., *Co-Administration of Paroxetine and Pravastatin Causes Deregulation of Glucose Homeostasis in Diabetic Rats via Enhanced Paroxetine Exposure*, 35 ACTA PHARMACOLOGICA SINICA 792, 792–93 (2014).

207. The Paxil-Pravachol interaction was only identified through post-market data mining. *Id.*

irritating the tissue at the injection site, even where the injection is very brief. Where an infusion pump uses an indwelling catheter to inject a drug to a site for a prolonged period of time, the risk of irritation and its magnitude, should it occur, are larger.²⁰⁸ But the existence of these risks is foreseeable, because they are posed by the individual constituents of the combination product.

More concerning are the qualitative synergistic risks posed by combination products. Cases involving drug-eluting stents²⁰⁹ are illustrative. Drug-eluting stents were developed because coronary arteries opened with “bare metal” stent devices tended to become obstructed within weeks to a few months as the cells that form the innermost layer of the artery began to divide and grow rapidly in a process called neo-intimal hyperplasia.²¹⁰ Combining an antiproliferative drug, which prevents cell growth, with a stent device prevents neo-intimal hyperplasia, resulting in superior rates of artery patency.²¹¹ Paclitaxel, or Taxol, is one of the antiproliferative drugs that was used in the first generation of drug eluting stents.²¹² By itself, Paclitaxel is associated with a very low risk of arterial thrombosis, and is not associated with thrombosis occurring late (such as months to years) after drug administration.²¹³ Likewise, “bare metal stents,” stents without the antiproliferative coating, had not been associated with late thrombosis.²¹⁴ But the first generation drug-eluting stent that used Taxol (the “Taxus”) was found to have a risk of late-occurring in-stent thrombosis, which was associated with a high mortality rate.²¹⁵ This risk was unexpected: neither constituent alone was associated

208. *Cf.* *Stengel v. Medtronic, Inc.*, 704 F.3d 1224, 1227 (9th Cir. 2012) (en banc) (describing paralysis resulting from drug infusion via an indwelling catheter that resulted from tissue irritation).

209. *See supra* notes 182–192 and accompanying text.

210. Edoardo Camenzind, P. Gabriel Steg & William Wijns, *Stent Thrombosis Late After Implantation of First-Generation Drug-Eluting Stents; A Cause for Concern*, 115 *CIRCULATION* 1440, 1440 (2007).

211. *Id.*

212. Camenzind, Steg & Wijns, *supra* note 210, at 1440.

213. *See* FDA, DRUGS@FDA: FDA APPROVED PRODUCTS, NDA 020262 (1992) (discussing FDA labeling, which does not mention arterial thrombosis). Like FDA labeling, the medical literature does not contain reports of an increased risk of arterial thrombosis: I performed a search of the medical literature using the NIH’s PubMed search engine on May 29, 2018, using the keywords “paclitaxel” and “thrombosis” and “NOT stent.” *See* U.S. Nat’l Library of Med., Nat’l Inst. of Health, PUBMED, <https://www.ncbi.nlm.nih.gov/pubmed/> [<https://perma.cc/JZ2Q-89LC>]. PubMed returned no relevant hits.

214. Camenzind, Steg & Wijns, *supra* note 210, at 1440. *But see* Kyohei Yamaji et al., *Bare Metal Stent Thrombosis and In-Stent Neointimal Hyperplasia*, 5 *CIRCULATION: CARDIOVASCULAR INTERVENTIONS* 47, 47–48 (2012) (citing a 0.1% risk of very late thrombosis in bare metal stents).

215. Camenzind, Steg & Wijns, *supra* note 210, at 1440, 1443.

with late-occurring thrombosis, and even the pivotal study on which the FDA based the Taxus's approval failed to identify this risk.²¹⁶

Although the FDA and the scientific and clinical communities have decades of experience in identifying and evaluating risk synergies, this experience is mainly for quantitative synergies within specific product categories (for instance, drug-drug products). By contrast, combination products involve potential synergies created by different product types. As the drug-eluting stent example shows, combination products may be more likely to present risks that are qualitatively different from those presented by the individual constituents. The FDA and the scientific community have far less experience in identifying and characterizing these synergies.²¹⁷

As the discussion in this Section has demonstrated, combination products comprise a large and growing portion of all medical products, and their risks are unforeseeable. How should the calibrated regulatory system described in section I.C treat them? Given the presence of a new drug and the problem of qualitative synergistic risks, one would expect the federal layer of regulation to occur through the NDA process, with its robust information-forcing obligations. Further, one would expect the state layer of regulation to function as it does in regard to new drugs. But, as the next section demonstrates, neither of these has been the case.

B. Aaron v. Medtronic Inc. and the Regulatory Gap

The approval process for, injuries caused by, and litigation surrounding Medtronic's InFUSE/LT-CAGE combination product illustrate many aspects of the regulatory gap. This product is used to fuse adjacent vertebrae in the spines of patients with low back pain due to degenerative disk disease.²¹⁸ The product consists of a device, a thimble-shaped metallic cage, and a drug, recombinant bone morphogenic protein (rhBMP-2).²¹⁹ The cage

216. See FDA, P030025, SUMMARY OF SAFETY AND EFFECTIVENESS DATA: TAXUS EXPRESS CORONARY STENT SYSTEM 19 tb1.9 (2004), https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030025B.pdf [<https://perma.cc/M9ML-UHVF>].

217. See FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: EARLY DEVELOPMENT CONSIDERATIONS FOR INNOVATIVE COMBINATION PRODUCTS 2 (2006), <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126054.pdf> [<https://perma.cc/45HX-CHR9>] (“[A]lthough a combination product may be comprised of an already approved drug and an already approved device, new scientific and technical issues may emerge when the drug and device are combined or used together.”).

218. FDA, PMA No. P000058, SUMMARY OF SAFETY AND EFFECTIVENESS DATA (2002), https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf [<https://perma.cc/35VL-X6RF>].

219. See *Aaron v. Medtronic, Inc.*, 209 F. Supp. 3d 994, 998 (S.D. Ohio 2016); *supra* note 220, at 1.

holds the drug in place and “maintains the proper height between the vertebrae.”²²⁰ The rhBMP-2 promotes bone growth which fuses the adjacent vertebrae, stabilizing the spine.²²¹ Since 2013, thousands of plaintiffs have filed suits seeking compensation for physical injuries alleged to have arisen from the use of the InFUSE/LT-CAGE product.

At the time Medtronic sought FDA approval, the InFUSE/LT-CAGE appeared to offer a significant advantage over the traditional approach, which required surgeons to harvest bone fragments from the patient’s hip bone. Once implanted into the area of the degenerated disk, the bone fragments stimulated bone growth that stabilized the spine. The rhBMP-2 constituent stimulated spinal bone growth, eliminating the need for the painful harvesting procedure.

When Medtronic submitted the InFUSE/LT-CAGE combination product for approval, the rhBMP-2 constituent had not previously been subjected to the NDA process.²²² Thus, the drug constituent *and* the combination product as a whole arrived at the FDA with the large deficit in information regarding risk that accompanies most new drugs. Nonetheless, the FDA approved rhBMP-2, along with the other constituents of the InFUSE/LT-CAGE product, through the PMA process. This decision was within the agency’s statutory authority.²²³ But the decision perpetuated the information deficit because the FDA required Medtronic to generate less information about risk than an NDA approval would have required. Many other recombinant drugs, which had been approved through the NDA process, were supported by multiple, large, randomized, blinded clinical trials involving thousands of patients. For example, Novo/Nordisk obtained NDA approval for its diabetes drug,

220. Fact Sheet, Medtronic, Inc., *INFUSE® Bone Graft/LT-CAGE® Lumbar Tapered Fusion Device* (2013), <http://www.medtronic.com/content/dam/medtronic-com/us-en/newsroom/media-resources/media-kits/infuse-bone-graft-lt-cage-device/documents/medtronic-infuse-bone-graft-lt-cage-lumbar-tapered-fusion-device-fact-sheet.pdf> [<https://perma.cc/6RNJ-RXFJ>]. The product also includes a biological constituent (a collagen matrix) that acts as a scaffold for the rhBMP-2. *Id.* at 2.

221. See Kevin S. Cahill et al., Am. Med. Ass’n, *Prevalence, Complications, and Hospital Charges Associated with Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures*, 302 JAMA 58, 58–59 (2009).

222. Nor had rhBMP-2 been approved by any other regulatory body in the world. See *Infuse Bone Graft*, MEDTRONIC, <https://global.medtronic.com/xg-en/e/response/infuse-bone-graft.html> [<https://perma.cc/H9NP-43GS>] (noting that the first approval was by the FDA in 2002). The FDA first approved the InFUSE/LT-CAGE product on July 2, 2002. See *Premarket Approval (PMA)*, FDA, <https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma> [<https://perma.cc/3EEX-P2YP>]. The European Medicines Agency approved the product under the name *Inductos* on September 9, 2002. See *Inductos*, EUR. MEDS. AGENCY (2005), <https://www.ema.europa.eu/en/medicines/human/EPAR/inductos#authorisation-details-section> [<https://perma.cc/TQ5L-PW73>].

223. See *infra* section III.A.

Victoza, based on human studies, which included “[a] total of 3978 patients . . . in 5 double-blind . . . randomized, controlled clinical trials.”²²⁴ By contrast, the human data supporting rhBMP-2 consisted of a pilot study involving fourteen subjects and a single, non-randomized, non-blinded pivotal study of 427 subjects.²²⁵

The InFUSE/LT-CAGE product—based on the data required by the PMA process—did not appear to carry an increased risk of serious harm.²²⁶ But since its approval on July 2, 2002, the product has caused excessive bone growth in the spines of many patients, compressing the nearby nerves and resulting in intractable pain, paralysis, incontinence, and a host of other devastating complications.²²⁷ In 2011, *The Spine Journal* published the results of a systematic review of the medical literature and associated documents on rhBMP-2, which led the investigators to conclude that the original pilot and pivotal trials were inadequate to assess safety and marred by conflicts of interest.²²⁸ A review of subsequent publications suggested that the rate of adverse events ranged between 10% and 50%.²²⁹

The information deficits concerning the risks of rhBMP-2, which resulted from approval through the PMA process, might have been offset by tort and products liability failure-to-warn actions. But courts have mostly found these claims to be preempted at summary judgment, or even earlier. The Southern District of Ohio’s analysis in *Aaron v. Medtronic, Inc.*,²³⁰ is representative. In this consolidated action, several hundred patients alleged that they suffered intractable pain, inflammatory reactions, chronic radiculitis, retrograde ejaculation, sterility, and other complications caused by excessive bone growth.²³¹ The court granted

224. FDA, HIGHLIGHTS OF PRESCRIBING INFORMATION: VICTOZA (2010), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/0223411bl.pdf [<https://perma.cc/HN9U-FMRC>].

225. U.S. FOOD & DRUG ADMIN, P000058, SUMMARY OF SAFETY AND EFFECTIVENESS DATA: INFUSE BONE GRAFT/LT-CAGE LUMBAR TAPERED FUSION DEVICE 31 (2002), https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058B.pdf [<https://perma.cc/ZJ58-H4MA>].

226. *Id.* at 8 (“The reported rates of several adverse events were high, but similar, in both the investigational and control groups.”).

227. *See, e.g.*, Complaint for Damages at 77–79 ¶¶ 250–57, *Alton v. Medtronic, Inc.*, 970 F. Supp. 2d 1069 (D. Or. 2013) (No. 3:13-cv-00409-PK).

228. Eugene J. Carragee, Eric L. Hurwitz & Bradley K. Weiner, *A Critical Review of Recombinant Human Bone Morphogenetic Protein-2 Trials in Spinal Surgery: Emerging Safety Concerns and Lessons Learned*, 11 *SPINE J.* 471, 474, 485 (2011).

229. *Id.* at 471.

230. *Aaron v. Medtronic, Inc.*, 209 F. Supp. 3d 994 (S.D. Ohio 2016).

231. Plaintiffs’ Memorandum in Opposition to Defendants’ Motion to Dismiss, *Aaron*, 209 F. Supp. 3d at 994.

Medtronic's motion to dismiss under Federal Rule of Procedure 12(b)(6), finding plaintiffs' failure-to-warn claims preempted.²³² The court assumed that the InFUSE/LT-CAGE combination product, including the rhBMP-2 protein, is a Class III medical device.²³³ Observing that a state failure-to-warn verdict would require Medtronic to provide a stronger warning, which would be "different from, or in addition to" the labeling required by the FDA, the court held that section 360k of the Medical Device Amendments expressly preempted these claims.²³⁴ Dismissal at this early stage precluded discovery, which might have unearthed information regarding the risks of rhBMP-2. Thus, neither the federal nor the state layer of regulation functioned to promote the generation and dissemination of risk information concerning the rhBMP-2 constituent as robustly as they would have had the InFUSE/LT-CAGE product been approved through the NDA process.

The lower courts have confronted preemption defenses in nearly fifty InFUSE/LT-CAGE tort and products liability cases involving thousands of plaintiffs. As in *Aaron*, most courts have held that PMA approval preempts state law failure-to-warn claims.²³⁵ Courts have found claims to

232. *Aaron*, 209 F. Supp. 3d at 1006.

233. *Id.* at 997–98.

234. *Id.* at 1004.

235. See, e.g., *Caplinger v. Medtronic, Inc.*, 784 F.3d 1335 (10th Cir. 2015); *Aaron*, 209 F. Supp. 3d at 994; *Anderson v. Medtronic, Inc.*, No. 14–cv–00615–BAS(RBB), 2015 WL 2115342, at *7 (S.D. Cal. May 6, 2015); *Byrnes v. Small*, 60 F. Supp. 3d 1289 (M.D. Fla. 2015); *Jones v. Medtronic, Inc.*, 89 F. Supp. 3d 1035 (D. Ariz. 2015); *Mendez v. Shah*, 94 F. Supp. 3d 633 (D.N.J. 2015); *Thorn v. Medtronic Sofamor Danek, USA, Inc.*, 81 F. Supp. 3d 619 (W.D. Mich. 2015); *Wright v. Medtronic, Inc.*, 81 F. Supp. 3d 600 (W.D. Mich. 2015); *Arthur v. Medtronic, Inc.*, No. 4:14–CV–52 (CEJ), 2014 WL 3894365 (E.D. Mo. Aug. 11, 2014); *Arvizu v. Medtronic, Inc.*, 41 F. Supp. 3d 783 (D. Ariz. 2014); *Blankenship v. Medtronic, Inc.*, 6 F. Supp. 3d 979 (E.D. Mo. 2014); *Brady v. Medtronic, Inc.*, No. 13–cv–62199–RNS, 2014 WL 1377830, at *8 (S.D. Fla. Apr. 8, 2014); ; *Coleman v. Medtronic, Inc.*, 223 Cal.App.4th 413 (Cal. Ct. App. 2014); *Dunbar v. Medtronic, Inc.*, No. CV 14–01529–RGK (AJWx), 2014 WL 3056026 (C.D. Cal. June 25, 2014); *Eidson v. Medtronic, Inc.*, 40 F. Supp. 3d 1202 (N.D. Cal. 2014); *Hawkins v. Medtronic, Inc.*, No. 1:13–CV–00499 AWI SKO, 2014 WL 346622, at *14 (E.D. Cal. Jan. 30, 2014); *Martin v. Medtronic, Inc.*, 63 F. Supp. 3d 1050 (D. Ariz. 2014); *McCormick v. Medtronic, Inc.*, 101 A.3d 467 (Md. Ct. Spec. App. 2014); *Scanlon v. Medtronic Sofamor Danek, USA, Inc.*, 61 F. Supp. 3d 403 (D. Del. 2014); *Schouest v. Medtronic, Inc.*, 13 F. Supp. 3d 692 (S.D. Tex. 2014); *Scovil v. Medtronic, Inc.*, 995 F. Supp. 2d 1082 (D. Ariz. 2014); *Zaccarello v. Medtronic, Inc.*, 38 F. Supp. 3d 1061 (W.D. Mo. 2014); *Alton v. Medtronic, Inc.*, 970 F. Supp. 2d 1069 (D. Ore. 2013); *Dawson v. Medtronic, Inc.*, C/A No. 3:13–cv–663–JFA, 2013 WL 4048850, at *6 (D.S.C. Aug. 9, 2013); *Houston v. Medtronic, Inc.*, 957 F. Supp. 2d 1166 (C.D. Cal. 2013); *Kashani-Matts v. Medtronic, Inc.*, No. SACV 13–01161–CJC(RNBx), 2013 WL 6147032, at *4 (C.D. Cal. Nov. 22, 2013); *Ledet v. Medtronic, Inc.*, No. 1:13CV200–LG–JMR, 2013 WL 6858858 (S.D. Miss. Dec. 30, 2013); *Otis-Wisher v. Fletcher Allen Health Care, Inc.*, 951 F. Supp. 2d 592 (D. Vt. 2013); *Angeles v. Medtronic, Inc.*, 863 N.W.2d 404 (Minn. Ct. App. 2015). Other cases with the same outcome involved state statutory protections. *Lyles v. Medtronic, Inc.*, Docket No.: 3:15–cv–00910, 2015 WL 9997860 (W.D. La. Nov. 23, 2014); *Smith v. Medtronic,*

be preempted even where the plaintiffs alleged that only the drug constituent was used.²³⁶ In the few cases where courts held that plaintiffs' failure-to-warn claims were not preempted, the basis was that Medtronic had engaged in off-label promotion of the product; in these cases the courts still assumed that InFUSE/LT-CAGE was a device.²³⁷

The impact of these cases is unmistakable: new drugs—the adverse effects of which cannot be adequately predicted and characterized prior to broad human exposure—can be approved by the FDA based on the relatively limited data required for device approvals provided the manufacturer submits the new drug as a constituent of a combination product that also contains a high-risk device.²³⁸ This is true, even though the risks posed by new drugs incorporated into drug-device combination medical products may be more difficult to predict than the risks posed by any other category of medical products. And, in courts that adopt the majority approach illustrated by *Aaron*, state tort and products liability actions are preempted by application of Section 360k, eliminating the information-producing incentives that state law might otherwise provide. Thus, the information deficits presented by some combination products are not remedied by the rigorous two-layered regulatory regime to which new drugs are subjected. It is this truncated function of both federal and state information forcing that this Article refers to as a “regulatory gap.” As a result of this gap, new drugs may reach patients with significant deficits in risk information. Given the current trends, the number of these new drugs can be expected to increase as manufacturers increasingly shift to developing combination products.

These cases illustrate the fact that combination product approval may subvert the emergent, calibrated information-forcing system of federal and state regulation set out in section I.C. The next part explores in detail

Inc., Civil Action No. 13–451, 2014 WL 2547813 (W.D. La. June 4, 2014); *Gavin v. Medtronic, Inc.*, No. 12–0851, 2013 WL 3791612 (E.D. La. July 19, 2013).

236. *See, e.g., Ramirez v. Medtronic, Inc.*, 961 F. Supp. 2d 977, 983 (D. Ariz. 2013) (“When Dr. Wang performed Ramirez’s lumbar fusion operation, he used only the rhBMP–2 bone graft component of the Infuse device. . . .”); Amended Complaint at ¶ 21, *Aaron*, 209 F. Supp. 3d 994 (noting that the surgeon “uses BMP-2 with and without a cage”); First Amended Complaint at ¶ 250, *Angeles*, 863 N.W.2d 404 (“MEDTRONIC packaged and sold the LT-Cage independently from the Infuse®> Bone Graft Kit so that the Infuse® kit could be used either with other cages or without a cage at all.”). The cage and the rhBMP-2 are packaged separate from one another.

237. *Norabuena v. Medtronic, Inc.*, 86 N.E.3d 1198 (Ill. App. Ct. 2017); *Garross v. Medtronic, Inc.*, 77 F. Supp. 3d 809 (E.D. Wis. 2015); *Ramirez v. Medtronic Inc.*, 961 F. Supp. 2d 977 (D. Ariz. 2013); *Beavers-Gabriel v. Medtronic, Inc.*, Civ. No. 13–00686 JMS–RLP, 2015 WL 143944 (D. Haw. Jan. 9, 2015); *Hornbeck v. Medtronic, Inc.*, 13 C 7816, 2014 WL 2510817 (N.D. Ill. June 2, 2014).

238. Industry participants and consultants openly recognize the practical benefits of seeking FDA approval through the device rather than the drug pathways. *See, e.g., Drues, supra* note 34 (“CDRH is the easiest regulatory path through the FDA.”).

how the regulatory gap itself has emerged.

III. THE REGULATORY GAP IN DRUG-DEVICE COMBINATION PRODUCT APPROVAL

This Part examines the immediate causes of the regulatory gap, beginning with the federal side of the gap in section III.A. Approving new drugs (such as rhBMP-2) through the PMA process instead of the NDA process is an exercise of discretion that is within the FDA's statutory authority. In granting that authority, Congress was addressing policy considerations far removed from the information-forcing functions of the NDA process. Turning to the state side of the gap, neither Congress nor the FDA nor the Supreme Court has addressed whether federal regulation of combination products preempts state tort and product liability actions. Nonetheless, as section III.B shows, most courts in cases involving the Infuse/LT-Cage product, drug eluting stents, and other drug-device combination products have found state law to be expressly preempted. Section III.B argues that in their preemption analyses, these courts have assumed the answers to three key questions regarding the appropriate construction of the term "combination product" and the preemptive reach of the express preemption provision of the MDA. These assumptions lead to outcomes that subvert the information-forcing regulatory system that Part I described.

A. *Federal Regulation of Combination Products: The Federal Side of the Gap*

Congress first addressed the regulation of combination products in the Safe Medical Devices Act of 1990 ("SMDA," or "Act").²³⁹ Section 16 of the Act amended the FDCA, which at the time contained distinct regulatory regimes for prescription drugs, medical devices, and biological products. Under that earlier regime, a manufacturer of a combination product had to obtain approval for each individual constituent of the product.²⁴⁰ Section 16 directed the Secretary of Health and Human Services (HHS) to "designate a component of the [FDA] to regulate products that constitute a combination of a drug, device, or biological product."²⁴¹ The Act requires the FDA to choose a single component, or

239. Pub. L. No. 101-629, § 16, 104 Stat. 4526 (1990) (codified at 21 U.S.C. § 353(g) (2012)).

240. BERNARD D. REAMS, JR., SAFE MEDICAL DEVICES ACT OF 1990: A LEGISLATIVE HISTORY OF PUBLIC LAW NO. 101-629, at 31 (1996).

241. § 16, 104 Stat. at 4526 (emphasis added). "Agency component" refers to the various sub-Agency "centers," each of which is responsible for the regulation of a certain category of products.

regulatory center, determined by “the primary mode of action of the combination product,”²⁴² which the FDA interprets to mean “the single mode of action of a combination product that provides the most important therapeutic action of the combination product.”²⁴³

The SMDA created a regulatory regime for combination products that is fundamentally different from the regimes that govern non-combination drugs and devices. For non-combination products, determining the statutory definition entails assigning the same regulatory identity—in general, a product defined as a drug will be regulated as a drug, and a product defined as a device will be regulated as a device.²⁴⁴ But the combination products regime splits statutory definition and regulatory identity. The FDA first determines a product’s statutory identity (“[Classifying] . . . the product as a drug, biological product, device, or a combination product . . .”).²⁴⁵ For combination products, the agency then assigns a regulatory identity (“the component of the Food and Drug Administration that will regulate the product”) based on the primary mode of action.²⁴⁶ A product that meets the statutory definition of a drug, when incorporated into a drug-device combination product, may not necessarily provide “the most important therapeutic action.”²⁴⁷ Under Section 16, such a drug, along with the other constituents of a combination product, will be assigned to CDRH for premarket evaluation under the agency’s device authorities.

See supra note 47. Under the SMDA, the designated center is then responsible for premarket review and subsequent regulation over the entire life cycle of the product.

242. *Id.*

243. 21 C.F.R. § 3.2(m) (2019).

244. Illustrating the importance of a product’s statutory identity, in cases that predate the MDA, the FDA defined some devices as drugs in order to bring those devices within the Agency’s drug regulatory authority. *See supra* note 55 and accompanying text; *see also* AMP Inc. v. Gardner, 389 F.2d 825 (2d Cir. 1968) (FDA defining nylon ligature as a drug); United States v. 48 Dozen Packages, etc., 94 F.2d 641 (2d Cir. 1938) (FDA defining gauze bandages as drugs). The MDA addressed these “transitional devices,” ordering the FDA to engage in notice-and-comment rulemaking in order to reclassify them as Class III devices. Medical Device Amendments of 1976, Pub. L. No. 94-295, § 520(l), 90 Stat. 572 (1976) (codified as amended at 21 U.S.C. § 355 (2012)).

245. FDA Modernization Act of 1997, Pub. L. No. 105-115, § 416(a), 111 Stat. 2378 (1997) (codified as amended at 21 USC § 360bbb-2 (2012)).

246. *See id.*

247. 21 C.F.R. § (3)(1)(m). For example, the primary intended purpose of a drug-eluting stent is to maintain the patency of a coronary artery. Both the stent device and the antiproliferative drug contribute to this effect. However, the FDA has determined that the device mode of action—the physical action of the stent—contributes more to the primary intended purpose of keeping the artery open than does the drug mode of action. *Jurisdictional Update: Drug Eluting Cardiovascular Stents*, FDA (2018), <https://www.fda.gov/combination-products/jurisdictional-updates/jurisdictional-update-drug-eluting-cardiovascular-stents> [<https://perma.cc/QGV4-4MSK>].

The FDA Modernization Act of 1997 (FDAMA)²⁴⁸ highlighted the distinct features of combination products regulation. FDAMA created a process through which manufacturers can “submit a request to the Secretary respecting the classification of the product as a drug, biological product, device, or a combination product . . . *or* respecting the component of the Food and Drug Administration that will regulate the product.”²⁴⁹ FDA regulations and guidance documents confirm that the Agency views the determination of a combination product’s statutory definition and its regulatory identity as two separate acts.²⁵⁰ Implementing FDAMA, the FDA also created an informal “pre-RFD” through which a manufacturer can obtain a “nonbinding assessment of the regulatory identity or classification of a product as a drug, device, biological product, or combination product.”²⁵¹

The 21st Century Cures Act,²⁵² which was enacted in 2016, reinforces the unique structure of the combination products regulatory regime. The Cures Act prohibits the FDA from determining the primary mode of action of a combination product, and thus the assignment of a regulatory identity of a combination product, “solely because the combination product has *any* chemical action within or on the human body.”²⁵³ The Cures Act clarifies that different rules now determine the assignment of regulatory identities for combination products and for drugs and devices.²⁵⁴ The FDA may define and regulate a non-combination product as a drug if chemical action supplies any of the means through which it achieves its primary purpose. By contrast, for a combination product—including its drug constituents—to be regulated as a drug, chemical action must “make the greatest contribution to the overall intended [] effects”²⁵⁵ Thus, some products that exert drug action, which would

248. FDA Modernization Act of 1997, Pub. L. No. 105-115, § 416, 111 Stat. 2296 (1997) (codified at 21 U.S.C. § 301 (2012)).

249. *Id.* (emphasis added).

250. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: HOW TO WRITE A REQUEST FOR DESIGNATION (RFD) 3 (2011), <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf> [<https://perma.cc/V9FV-7U9E>] (noting that requests for designation may seek a determination of “the regulatory identity or classification of a product as a drug, device, biological product, or combination product”).

251. FDA, GUIDANCE FOR INDUSTRY: HOW TO PREPARE A PRE-REQUEST FOR DESIGNATION (PRE-RFD) (2018), <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm534898.pdf> [<https://perma.cc/J6FY-JUM5>].

252. 21st Century Cures Act, Pub. L. No. 114-255, §§ 3038, 503(g), 130 Stat. 1033, 1105 (2016).

253. *Id.* at 1106 (emphasis added).

254. *Id.*

255. *Id.*

be required to undergo rigorous NDA approval if submitted as a non-combination product, may be approved under the less-rigorous PMA process if submitted as part of a combination product.

The determination of a medical product's statutory identity and of a combination product's primary mode of action are exercises of an expert agency's statutorily conferred discretion. Courts typically grant the FDA's decisions on these matters strong, *Chevron*-type deference²⁵⁶ under which courts defer to any reasonable agency interpretation of an ambiguous statute.²⁵⁷ Further, the FDCA now incorporates a default in favor of the manufacturer's preferred assignment of a regulatory identity. By statute, a manufacturer may "suggest" the regulatory identity the FDA should assign its product.²⁵⁸ Because the device pathways are less costly, lengthy, and demanding, manufacturers will most often suggest to the FDA that it assign a regulatory identity of a device.²⁵⁹ The agency has a short sixty-day window in which to disagree, after which the manufacturer's suggested identity becomes binding on the agency.²⁶⁰ Thus, the premarket evaluation of new drugs submitted as constituents of combination products will be channeled into the PMA pathway, creating the federal side of the regulatory gap. As a result of this channeling, the information-forcing functions served by the FDA's premarket evaluation of some new drugs has been constrained, as the history of the rhBMP-2 constituent of the Infuse/LT-Cage product illustrates.²⁶¹

B. Lower Courts and Preemption: The State Side of the Gap

In recent years, the lower federal and state courts have created the state side of the regulatory gap by endorsing preemption defenses in a growing number of tort and products liability cases involving the Infuse/LT-Cage product, drug eluting stents, transdermal patches, and other drug-device combination products. As this section argues, the courts in these cases have had little to guide their preemption analyses. Congress did not expressly preempt state law claims against combination products

256. 467 U.S. 837 (2984).

257. *See* *Prevor v. FDA*, 67 F. Supp. 3d 125, 137 (D.D.C. 2014) (stating that *Chevron* deference applies to FDA determinations of primary mode of action). Where the *Chevron* analysis of an agency's interpretation of a statute finds the statute itself to be ambiguous, empirical data have shown that the agency's view prevailed in over 90% of cases. Kent Barnett & Christopher J. Walker, *Chevron in the Circuit Courts*, 116 MICH. L. REV. 1, 35 fig.3 (2017).

258. 21 U.S.C. § 360bbb-2(c) (2012).

259. *See Drues, supra* note 34.

260. 21 U.S.C. § 360bbb-2(c).

261. *See supra* notes 224–229 and accompanying text.

manufacturers in the SMDA or in any subsequent legislation. Nor has Congress explicitly applied section 360k, the medical device express preemption provision, to combination products. Further, the FDA has not provided its view as to whether its regulation of combination products preempts state law. Nor has the Supreme Court addressed this question.²⁶² Nonetheless, courts have almost always found that FDA approval preempts tort and product liability failure-to-warn claims. These decisions have created the state side of the regulatory gap.

For example, in *Riley v. Cordis Corp.*²⁶³ the plaintiff suffered a heart attack after doctors placed a “Cypher,” a drug-eluting stent made by Cordis, into one of his coronary arteries. He brought claims against Cordis under Minnesota law, including negligence and strict products liability failure-to-warn claims.²⁶⁴ The Cypher was a first-generation drug-eluting stent that consisted of a PMA-approved stent device coated in Sirolimus, an NDA-approved drug.²⁶⁵ First generation drug-eluting stents were associated with a novel complication: “late in-stent thrombosis,” the development of a blood clot inside the stent years after the stent was placed.²⁶⁶ Riley’s heart attack occurred two years after his physicians placed the Cypher into his coronary artery. He argued that had Cordis adequately warned about the risk of late in-stent thrombosis, his doctors would have ordered his treatment with two or more blood thinners to have continued indefinitely, which would have prevented his heart attack.²⁶⁷

The court held that section 360k expressly preempted the failure-to-warn claims.²⁶⁸ Attempting to avoid preemption, Riley urged that in its preemption analysis the court should treat the Cypher as an aggregation of individual constituents, each subject to its own preemption rules.²⁶⁹ In

262. The Court’s only mention of combination products came in *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000), where the majority opinion referred to cigarettes as “so-called ‘combination products’” or simply enclosed the term within quotation marks. *Id.* at 125–27, 129 (quoting 21 U.S.C. § 353(g)(1)). The dissent appeared to view a combination product as a device that contains a drug. *Id.* at 175 (Breyer, J., dissenting) (“‘[C]ombination product’—i.e., a ‘device’ (such as a cigarette) that contains a ‘drug’ (such as nicotine).”).

263. 625 F. Supp. 2d 769 (D. Minn. 2009).

264. *Id.* at 773.

265. Cordis licensed the brand version of sirolimus, Rapamune, from the patent and NDA holder, Wyeth. See *CYPHER(R) Sirolimus-Eluting Coronary Stent Receives FDA Approval for MRI Scans Immediately Following Implantation*, PR NEWSWIRE (Apr. 20, 2005), <https://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/cypherr-sirolimus-eluting-coronary-stent-receives-fda-approval> [<https://perma.cc/KS2T-BUGL>].

266. See *supra* notes 212–216 and accompanying text.

267. *Riley v. Cordis Corp.*, 625 F. Supp. 2d 769, 780 (D. Minn. 2009).

268. *Id.* at 783.

269. *Id.* at 779–80 (“Riley also argues that, because the Cypher stent is coated with a drug, the

Riley’s view, the new drug constituent of the Cypher had caused the heart attack. Under *Wyeth*, a failure-to-warn claim arising from the new drug itself would not have been preempted.²⁷⁰ The court rejected this argument. Instead, the court made the first of three key assumptions that are characteristic of courts’ preemption analyses in the combination products cases. The court stated without explanation or analysis that the Cypher was a single entity, “a compound of mechanical and chemical parts that work together.”²⁷¹ Courts in the majority of combination products cases have agreed—usually without discussion—that combination products are single entities.²⁷²

Physically, drug eluting stents are indeed single entities. The stent and the antiproliferative coating cannot be separated and used individually. But courts have also made the single entity assumption in most of the Infuse/LT-Cage cases as well, even though the drug constituent (rhBMP-2) is manufactured and packaged separately from the device (LT-Tapered Cage). And courts have made this assumption even where plaintiffs have alleged that their physicians had used *only* the rhBMP-2 constituent.²⁷³

The *Riley* Court’s second key assumption is that in a preemption analysis a combination product is considered to be either a drug or a device, determined by the regulatory identity which the FDA has assigned. But as section III.A has shown, this is not the only identity that may be relevant: Combination products also have a statutory identity—under the FDCA they are defined as combination products, not as drugs or devices.²⁷⁴ Without confronting this question, the *Riley* court assumed that the Cypher was a device, noting that the “mechanical and chemical parts [] work together as

preemption analysis of § 360k(a) is inapplicable, and the Court must instead undertake the implied-preemption analysis that applies to claims relating to federally regulated drugs [under *Wyeth*].”).

270. See *supra* notes 109–111 and accompanying text.

271. *Riley*, 625 F. Supp. 2d. at 779 (emphasis added).

272. *Lauricella v. Cordis Corp.*, No. C 07-2016 SBA (PR), 2010 WL 2673328, at *1 (N.D. Cal. 2010) (“[A]n allegedly defective medical device known as ‘Cypher.’”); *Cordis Corp. v. O’Shea*, 24 So. 3d 576, 577 (Fla. App. 2009) (“The Cypher stent is considered a Class III medical device. . . .”); *McQuiston v. Boston Sci. Corp.*, No. 07–1723, 2009 WL 4016120, at *4 (W.D. La. Nov. 19, 2009) (“[T]he TAXUS Stent is a Class III device.”); *Angeles v. Medtronic, Inc.*, 863 N.W.2d 404, 410 (Minn. Ct. App. 2015); *Cornett v. Johnson & Johnson*, 48 A.3d 1041, 1051 (N.J. 2012) (“Class III devices, like the Cypher® stent. . . .”); *Cornett v. Johnson & Johnson*, 998 A.2d 543, 547 (N.J. Super. A.D. 2010) (“[A]lleged defects in a medical device, the Cypher® Sirolimus–Eluting Coronary Stent. . . .”).

273. *Aaron v. Medtronic, Inc.*, 209 F. Supp. 3d 994, 999 (S.D. Ohio 2016); *Ledet v. Medtronic, Inc.*, No. 1:13CV200-LG-JMR, 2013 WL 6858858, at *1 (S.D. Miss. Dec. 30, 2013); *Alton v. Medtronic, Inc.*, 970 F. Supp. 2d 1069, 1075 (D. Ore. 2013).

274. See *supra* notes 244–247 and accompanying text.

a single *medical device*.”²⁷⁵ Courts in other drug eluting stent cases have done the same.²⁷⁶ Likewise, in the Infuse/LT-Cage cases courts have typically assumed that the product is a “medical device,”²⁷⁷ or a “Class III medical device.”²⁷⁸ Only rarely have courts recognized that drug-eluting stents and the Infuse/LT-Cage product are statutorily defined as combination products. Often, the plaintiffs’ themselves characterized the combination product by the regulatory identity assigned by the FDA.²⁷⁹ But

275. *Riley*, 625 F. Supp. 2d at 779 (emphasis added).

276. *See supra* note 272.

277. *See generally* *Caplinger v. Medtronic, Inc.*, 784 F.3d 1335 (10th Cir. 2015); *Aaron v. Medtronic, Inc.*, 209 F. Supp. 3d 994 (S.D. Ohio 2016); *Anderson v. Medtronic, Inc.*, No. 14-cv-00615-BAS(RBB), 2015 WL 2115342 (S.D. Cal. May 6, 2015); *Byrnes v. Small*, 60 F. Supp. 3d 1289 (M.D. Fla. 2015); *Jones v. Medtronic*, 89 F. Supp. 3d 1035 (D. Ariz. 2015); *Lyles v. Medtronic, Inc.*, No. 3:15-cv-00910, 2015 WL 9997860 (W.D. La. Nov. 23, 2015); *Mendez v. Shah*, 94 F. Supp. 3d 633 (D.N.J. 2015); *Thorn v. Medtronic Sofamor Danek, USA, Inc.*, 81 F. Supp. 3d 619 (W.D. Mich. 2015); *Wright v. Medtronic, Inc.*, 81 F. Supp. 3d 600 (W.D. Mich. 2015); *Arthur v. Medtronic, Inc.*, No. 4:14-CV-52 (CEJ), 2014 WL 3894365 (E.D. Mo. Aug. 11, 2014); *Arvizu v. Medtronic Inc.*, 41 F. Supp. 3d 783 (D. Ariz. 2014); *Blankenship v. Medtronic, Inc.*, 6 F. Supp. 3d 979 (E.D. Mo. 2014); *Brady v. Medtronic, Inc.*, No. 13-cv-62199-RNS, 2014 WL 1377830 (S.D. Fla. Apr. 8, 2014); *Dunbar v. Medtronic, Inc.*, No. CV 14-01529-RGK (AJWx), 2014 WL 3056026 (C.D. Cal. June 25, 2014); *Eidson v. Medtronic, Inc.*, 40 F. Supp. 3d 1202 (N.D. Cal. 2014); *Hawkins v. Medtronic, Inc.*, No. 1:13-CV-00499 AWI SKO, 2014 WL 346622 (E.D. Cal. Jan. 30, 2014); *Martin v. Medtronic, Inc.*, 63 F. Supp. 3d 1050 (D. Ariz. 2014); *Scanlon v. Medtronic Sofamor Danek USA Inc.*, 61 F. Supp. 3d 403 (D. Del. 2014); *Schouest v. Medtronic, Inc.*, 13 F. Supp. 3d 692 (S.D. Tex. 2014); *Scovil v. Medtronic, Inc.*, 995 F. Supp. 2d 1082 (D. Ariz. 2014); *Zaccarello v. Medtronic, Inc.*, 38 F. Supp. 3d 1061 (W.D. Mo. 2014); *Alton v. Medtronic, Inc.*, 970 F. Supp. 2d 1069 (D. Or. 2013); *Dawson v. Medtronic, Inc.*, C/A No. 3:13-cv-663-JFA, 2013 WL 4048850 (D.S.C. Aug. 9, 2013); *Houston v. Medtronic, Inc.*, 957 F. Supp. 2d 1166 (C.D. Cal. 2013); *Kashani-Matts v. Medtronic, Inc.*, No. SACV 13-01161-CJC(RNBx), 2013 WL 6147032 (C.D. Cal. Nov. 22, 2013); *Ledet v. Medtronic, Inc.*, No. 1:13CV200-LG-JMR, 2013 WL 6858858 (S.D. Miss. Dec. 30, 2013); *Otis-Wisher v. Fletcher Allen Health Care, Inc.*, 951 F. Supp. 2d 592 (D. Vt. 2013); *Angeles v. Medtronic, Inc.*, 863 N.W.2d 404 (Minn. Ct. App. 2015); *Coleman v. Medtronic, Inc.*, 223 Cal. App. 4th 413 (Cal. Ct. App. 2014); *McCormick v. Medtronic, Inc.*, 219 Md. App. 485 (2014). Other cases with the same outcome involved state statutory protections. *See Smith v. Medtronic, Inc.*, No. 13-451, 2014 WL 2547813 (W.D. La. June 4, 2014); *Gavin v. Medtronic, Inc.*, No. 12-0851, 2013 WL 3791612 (E.D. La. July 19, 2013).

278. *See, e.g., Aaron*, 209 F. Supp. at 998 (“Infuse, like all medical devices sold in the United States.”); *Anders v. Medtronic, Inc.*, No. 4:14CV00194 ERW, 2014 WL 1652352, at *1 (E.D. Mo. Apr. 24, 2014); *Hawkins*, 2014 WL 346622 at *1; *Alton*, 970 F. Supp. at 1074 (describing Infuse/LT-Cage as a Class III medical device).

279. *See Lauricella v. Cordis Corp.*, No. C 07-2016 SBA (PR), 2010 WL 2673328, at *1 (N.D. Cal. July 2, 2010) (“[Plaintiff’s] complaint alleges that Defendant, a Florida corporation, is liable for designing and/or manufacturing an allegedly defective medical device known as ‘Cypher.’”); Plaintiff’s Amended Complaint at ¶ 7, *Caplinger*, 784 F.3d 1335 (describing Infuse as “a bio-engineered bone graft device”); Plaintiff’s Third Amended Complaint at ¶ 22, *O’Shea v. Cordis Corp.*, 24 So.3d 576 (Fl. Ct. App. 2008) (No. 4D09-1597) (“[T]he Cypher™ Sirolimus eluting stent was a medical device.”). *But see Garross v. Medtronic, Inc.*, 77 F. Supp. 3d 809, 815 (E.D. Wis. 2015) (noting that the “[p]laintiff contends [] that no federal requirements apply to the bone graft component itself because premarket approval applied only to the use of the components together”); *David v.*

even where plaintiffs have argued that the proper characterization of Infuse/LT-Cage combination product was something other than a “device,” courts have treated the product as a device.²⁸⁰

The *Riley* Court also made a third key assumption: that section 360k and the *Riegel* test apply to statutorily defined combination products that have been approved through the PMA pathway. The court found that section 360k expressly preempted the plaintiffs’ failure-to-warn claims against the manufacturer of a drug-eluting stent.²⁸¹ Likewise, in *Caplinger v. Medtronic, Inc.*,²⁸² the majority and dissent both applied the section 360k and *Riegel* framework to analyze the plaintiff’s state law claims against the manufacturer of the Infuse/LT-Cage product, never stopping to consider whether that framework was appropriate.²⁸³ Courts in most of the drug-eluting stent and Infuse/LT-Cage cases have relied on this assumption.²⁸⁴

These three assumptions determine the preemption outcomes that most courts have reached. The first assumption—that combination products are single entities and not mere aggregations of individual drugs and devices—is consistent with Congress’s conception of combination products as that conception has evolved since 1990, and with the FDA’s conception of these products since the Agency issued its final rule that implemented the SMDA. The other two assumptions, though, are difficult to support. Sections B.1 through B.3 examine each of these assumptions in turn, in order to determine whether the regulatory gap is a necessary result of federal regulation.

Medtronic, Inc., Case No. 13-cv-04441 DMG (CW), 2013 WL 12132038 at *4 (C.D. Cal. Aug. 6, 2013) (noting without deciding that “the Complaint alleges that Infuse is wrongfully categorized as a ‘device’ rather than a “combination product” under the FDCA”); *see also* Baker v. St. Jude Med., S.C., Inc., 178 S.W.3d 127, 130 (Tex. App. 2005) (regarding a prosthetic heart valve with an antibacterial silver coating, “[i]t is undisputed that a heart valve is a Class III medical device,” suggesting that plaintiffs simply accepted the FDA’s classification of the Silzone as a device).

280. *Angeles*, 863 N.W.2d at 409 (discussing plaintiff’s argument that the individual constituents of the Infuse product were not the same as the product itself, and thus were not subject to preemption under the medical device framework); *Aaron*, 209 F. Supp. 3d at 1003 (discussing the same).

281. *Riley v. Medtronic, Inc.*, 625 F. Supp. 2d 769, 781 (D. Minn. 2009).

282. 784 F.3d 1335, 1337 (10th Cir. 2015) (“Medtronic produces Infuse, a device that stimulates bone growth. . . .”).

283. *See id.* at 1340 (“There’s no dispute in our case that device-specific federal requirements apply to Infuse: the device endured the premarket approval process.”); *id.* at 1355 (Lucero, J., concurring in part and dissenting in part) (agreeing that *Riegel* applied but disagreeing with the outcome).

284. *See supra* note 233 and accompanying text.

I. Are Combination Products Single Entities or Do They Remain Aggregations of Individual Constituents?

The first assumption that most courts have made in the Infuse/LT-Cage and drug-eluting stent cases is that combination products are single entities.²⁸⁵ At stake is whether a single preemption analysis will determine the role of state law, or whether each constituent of the combination product will be subjected to its own preemption analysis. In the latter case, claims of harm arising from a PMA-approved device constituent would be preempted while claims of harm arising from a new drug constituent would not. State law would regulate only certain parts of a drug-device combination product.

The text of Section 16 of the Safe Medical Devices Act suggests that Congress originally conceived of combination products as aggregations of individual constituents as opposed to single entities. Section 16 refers to “products that constitute a combination of a drug, device, or biological product.”²⁸⁶ Understanding “constitute” to mean “[t]o give legal . . . form to (something)” or “[t]o make up or form,”²⁸⁷ Congress appears to have been directing the Secretary how to regulate the individual products that are combined by a manufacturer. The structure of the SMDA is also consistent with this conception. Ever since Congress enacted the FDCA in 1938, the product category definitions have been lodged in Section 321. But Section 16 expressly placed the description of combination products into 21 U.S.C. § 353, which has governed the labeling and distribution of drugs and devices. Thus, parts of the text and structure of Section 16 suggest that Congress did not conceive of combination products as a distinct product category, but rather as individual constituents intended for use together.

But other parts of Section 16 render Congress’s initial conception of combination products unclear. The title of Section 16 refers to *articles* made up of combinations of drugs, devices, and biologics.²⁸⁸ The FDCA uses the term “articles” to refer to the distinctly-defined product categories

285. See *supra* notes 269–273 and accompanying text.

286. Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16(a)(2), 104 Stat. 4511, 4526 (1990) (codified at 21 U.S.C. § 353 (2012)).

287. *Constitute*, BLACK’S LAW DICTIONARY (10th ed. 2014); accord THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (3d ed. 1995) (“To be the elements or parts of”); WEBSTER’S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE UNABRIDGED (3d ed. 2002) (“[T]he element or elements of which a thing . . . is made up.”).

288. Safe Medical Devices Act of 1990, Pub. L. No. 101-62, § 16, 104 Stat. 4511, 4526 (codified at 21 U.S.C. § 353(g) (2012)) (“Review of Market Applications for Articles Comprising Combinations of Drugs, Devices, and Biologics”).

that are regulated by the FDA, which at that time were drugs, devices, and biological products.²⁸⁹ Referring to a combination of individual constituents as an article suggests a conception of a combination product as a single entity, and by extension a conception of combination products as a fourth, distinct product category. The title describes these articles as “[c]omprising [c]ombinations of [d]rugs, [d]evices, and [b]iologics.”²⁹⁰ Understanding “comprise” to mean “to include” or “to consist of,”²⁹¹ the title purports to regulate articles—members of a category of products—that consist of some combination of drugs, devices, and biologics. The structure of the regime established by Section 16 also suggests an intent to regulate combination products as single entities. The amending language of Section 16 directs the Secretary to “determine the primary mode of action of *the combination product*.”²⁹² Once determined, the FDA must assign the product, and each of its constituents, to a single sub-Agency center for approval under a single pathway. Under this regime, the constituents are regulated at the federal level as parts of a single, complete entity.

Thus, the text, structure, and legislative history of the SMDA reveal an ambiguity in Congress’s original conception of combination products. This ambiguity did not create uncertainty as to which federal premarket regime should apply once the primary mode of action of a combination product was determined. But as explained below, the SMDA’s ambiguity leaves Congress’s intent toward the state layer of regulation uncertain.

By contrast, the FDA has consistently defined and referred to combination products as a distinct, *sui generis* product category. The FDA’s Final Rule implementing Section 16²⁹³ created a new section of the Code of Federal regulations that provides separate definitions for drugs, devices, biological products, *and* combination products.²⁹⁴ The rule consistently refers to combination products as a category distinct from

289. 21 U.S.C. §§ 321(f)–(i) (2012) (defining food, drugs, devices, and cosmetics in terms of “articles”).

290. Pub. L. No. 101-62, § 16, 104 Stat. 4511, 4526.

291. *Comprise*, WEBSTER’S THIRD NEW INTERNATIONAL DICTIONARY OF THE ENGLISH LANGUAGE UNABRIDGED (2002); *accord* THE AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (3d ed. 1995) (“To consist of . . . to include.”).

292. Pub. L. No. 101-62, § 16(a)(2), 104 Stat. 4511, 4526.

293. Assignment of Agency Component for Review of Premarket Applications, 56 Fed. Reg. 58,754 (Nov. 21, 1991).

294. 21 C.F.R. § 3.2(d)–(g) (2019).

drugs, devices, and biological products.²⁹⁵ FDA regulations implementing later congressional acts are consistent with this reading.²⁹⁶

Within a decade, Congress appears to have adopted the FDA's view of "combination products" as a fourth, distinct medical product category. The FDA Modernization Act of 1997 (FDAMA),²⁹⁷ speaks in terms of four distinct medical product categories. FDAMA created a process through which manufacturers can "submit a request to the Secretary respecting the classification of the product as a drug, biological product, device, or a combination product . . . or respecting the component of the Food and Drug Administration that will regulate the product."²⁹⁸ The Medical Device User Fee and Modernization Act of 2002 (MDUFMA)²⁹⁹ created what would become the current Office of Combination Products, charged with assigning "combination products to agency centers"³⁰⁰ The recently enacted 21st Century Cures Act³⁰¹ addresses combination products and medical devices in separate subtitles.³⁰² And the Cures Act requires a product sponsor to identify relevant products as combination products when the sponsor seeks any agency action.³⁰³

In spite of initial ambiguity, Congress appears to conceive of "combination products" as a distinct product category. The FDA has consistently conceived of combination products as a distinct category.

295. 21 C.F.R. § 3.3 (2019); *see also* 21 C.F.R. § 4.101 (2019) ("*Combination product applicant* means an applicant that holds the application(s) for a combination product.") (emphasis in original); 21 C.F.R. § 3.2(m) (2019) (defining primary mode of action as "the single mode of action of a *combination product* that provides the most important therapeutic action of the *combination product*") (emphasis added); Assignment of Agency Component for Review of Premarket Applications, *supra* note 293 (stating that the scope of the rule is not limited "to the combination products specified in the law" because "it also applies to any drug, device, or biological product where the jurisdiction is unclear or in dispute").

296. *See, e.g.*, 21 C.F.R. § 4.101 ("*Combination product applicant* means an applicant that holds the application(s) for a combination product."); *see also* 21 C.F.R. § 3.7(a)(1)–(2) (2019) (stating that sponsors of any drug, device, biological, or combination product may submit a request for designation of the center which will be assigned primary jurisdiction); 21 C.F.R. § 3.7(c)(2)(i) (2019) (stating that the sponsor of a combination or non-combination product seeking a designation must include in their request "[a] description of the product, including [the] [c]lassification, name of the product and all component products . . .").

297. Pub. L. No. 105-115 § 416, 11 Stat. 2378 (1997) (codified at 21 U.S.C. § 360bbb-2 (2012)).

298. *Id.*

299. Pub. L. No. 107-250, §§ 204, 503(g), 116 Stat. 1588, 1611 (2002).

300. *Id.*

301. 21st Century Cures Act, Pub. L. No. 114-255 sec. 3038, § 503(g), 130 Stat. 1033, 1105 (2016).

302. *Id.* (locating provisions applicable to combination products in Title III.D and provisions addressing devices in Title III.F).

303. *Id.* sec. 3038, § 503(a)(4). The Act requires a product sponsor to identify relevant products as combination products when the sponsor seeks any agency action with respect to the product. *Id.*

Both Congress and the FDA have consistently demonstrated the intent to regulate combination products as single entities as opposed to regulating them as individual constituents. This statutory and regulatory history supports courts' assumption that combination products are single entities. But this leaves unanswered the question of exactly what kind of single entity they are.

2. *Is Statutory Definition or Regulatory Identity Relevant in a Preemption Analysis?*

The second important assumption that courts have made in the Infuse/LT-Cage and drug-eluting stent cases is that a combination product is either a drug or a device, determined by the regulatory identity which the FDA has assigned.³⁰⁴ But this assumption overlooks a key aspect of combination products regulation: unlike drugs, devices, and biological products, for combination products the statutory definition and regulatory identity are two distinct attributes.³⁰⁵ The FDA Modernization Act of 1997 clarified the steps involved in assigning these attributes. The FDA first determines a product's statutory identity through its "classification of the product as a drug, biological product, device, *or a combination product*."³⁰⁶ Then the agency assigns a regulatory identity ("the component of the Food and Drug Administration that will regulate the product").³⁰⁷ For non-combination products, the assignment of a regulatory identity is determined by the statutory definition: a product that meets the statutory definition of a drug is regulated as a drug, while a product that meets the statutory definition of a device is regulated as a device. For combination products, though, the statutory definition does not determine the regulatory identity. Rather, the regulatory identity assignment is based on the primary mode of action, the determination of which is a separate step.³⁰⁸

304. *See supra* notes 275–280 and accompanying text.

305. *See supra* notes 244–247 and accompanying text.

306. Pub. L. 105-115, § 563(a), 111 Stat. 2378 (1997) (codified at 21 U.S.C. § 360bbb-2 (2012)) (emphasis added).

307. *Id.*

308. *See, e.g.*, FDA, GUIDANCE FOR INDUSTRY: HOW TO WRITE A REQUEST FOR DESIGNATION (RFD) 3 (2011), <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf> [<https://perma.cc/8ASB-88BH>] (noting that requests for designation may seek a determination of "the regulatory identity or classification of a product as a drug, device, biological product, or combination product . . .").

The 21st Century Cures Act reiterates the distinction between a product's statutory definition and regulatory identity.³⁰⁹ The Act also clarifies that there are different rules for assigning regulatory identities for combination products as compared with drugs and devices. The Act prohibits the FDA from determining the primary mode of action and thus the assignment of a regulatory identity of a combination product “solely because the combination product has any chemical action within or on the human body.”³¹⁰ For a non-combination product, the FDA may define the product and regulate it as a drug if chemical action supplies any of the means of achieving its primary purpose. By contrast, for a combination product to be regulated as a drug, chemical action must “make the greatest contribution to the overall intended [] effects.”³¹¹ Thus, some new products that exert drug action and pose the unforeseeable risks characteristic of new drugs—and which would be required to undergo rigorous NDA approval if submitted as a non-combination product—may be approved under the less-rigorous PMA process if submitted as a constituent of a combination product.

Unlike other medical products, all “combination products” thus have two identities.³¹² They are statutorily defined separately from drugs and devices, as “combination products.”³¹³ But they are regulated as drugs or devices.³¹⁴ By overlooking the fact that combination products have two identities, courts fail to address a key question: which identity is relevant in a preemption analysis? Nothing in the SMDA, FDAMA, or any other congressional act provides the answer. Nor has the FDA stated its views.

The answer may depend on whether a court was conducting an express or an implied preemption analysis. For an express preemption analysis, in which courts must determine the scope of a statutory provision, the answer lies in the specific statutory language, as discussed in section III.B.3. In an implied preemption analysis, especially an obstacle preemption analysis, the more likely answer is that the relevant identity is the product's regulatory identity as a drug or a device. If so, the existing drug and device frameworks forged in *Lohr*, *Buckman*, *Riegel*, *Wyeth*, *PLIVA*, and *Mutual Pharmaceuticals* would determine the analytic approach. However, if the relevant identity were the product's statutory identity—combination product—then courts would need to create a new implied preemption

309. *Id.* (requiring a product sponsor to identify relevant products as combination products when the sponsor seeks any agency action with respect to the product).

310. 21 U.S.C. § 353(g)(E).

311. 21 U.S.C. § 353(g)(C).

312. *See supra* notes 245–246 and accompanying text.

313. *Id.*

314. *Id.*

framework specific to combination products. Most courts in the Infuse/LT-Cage and drug-eluting stent cases have not reached this part of the analysis because they have assumed that failure-to-warn cases are expressly preempted by section 360k. The next section addresses this assumption.

3. *Does Section 360k Apply to Combination Products?*

The third assumption most courts have made is that the scope of the express preemption provision in the Medical Device Amendments extends to combination products.³¹⁵ Whether this is correct depends on whether Section 360k applies to products *defined* as medical devices or to products *regulated* as medical devices. Section 360k prohibits the states from “establish[ing] or continu[ing] in effect with respect to a device . . . any requirement which is different from, or in addition to, any requirement applicable under this chapter to the device, and which relates to the safety or effectiveness of the device.”³¹⁶

In determining the scope of this provision, as courts routinely note, “[t]he purpose of Congress is the ultimate touchstone.”³¹⁷ Unfortunately, neither a text-based, intent-based, nor purpose-based analysis affords a clear understanding of Congress’s purpose here. The plain text of the preemption provision refers to “a device” and “the device,” which seems most consistent with products statutorily defined as devices, not to products regulated as devices.³¹⁸ That is, had Congress intended Section 360k to extend to products regulated as devices, Congress could have included the words “regulated as” in the statute. But on closer analysis, this argument breaks down. When Congress drafted the MDA in 1976, a medical product’s statutory definition and its regulatory identity were congruent.³¹⁹ The determination that a product satisfied the statutory definition for devices entailed a determination that the product would be regulated as a device. The distinction between statutory definition and regulatory identity was not created for another fourteen years, when Congress passed the SMDA. And the distinction did not become relevant for another two decades, when manufacturers first began to assert preemption defenses in combination products failure-to-warn cases. The plain text is thus ambiguous.

315. *See supra* notes 281–283 and accompanying text.

316. 21 U.S.C. § 360k(a).

317. *Retail Clerks Int’l Ass’n v. Schermerhorn*, 375 U.S. 96, 103 (1963).

318. 21 U.S.C. § 360k(a).

319. *See supra* section I.A.

Nothing in the legislative history of the SMDA speaks directly to Congress's specific intent regarding the applicability of section 360k to failure-to-warn claims against combination products manufacturers.³²⁰ The limited legislative history concerning Section 16—mainly comments by the sponsors of the Senate's version of the Act—suggests that Section 16 was a response to industry complaints over the burdens created by the need to secure separate approvals for each constituent of a combination product.³²¹ Congress's focus was on ensuring a smooth federal approval process by permitting manufacturers to submit the individual constituents to a single approval process, instead of requiring separate approvals for each.³²² The best understanding is that no specific intent regarding preemption can be imputed to Congress as a whole, to the Act's sponsors, or to any other subset of legislators.

A purpose-based analysis is similarly unrewarding. Section 16 can be viewed as seeking to protect a then-fledgling and vulnerable combination products industry. By the time that Congress passed the SMDA, the benefits that drug-device combinations might offer had become apparent; it is reasonable to attribute a purpose of fostering the development of the combination products industry to the 101st Congress. Under this view, easing combination product manufacturers' premarket burdens by requiring only a single approval was simply the specific measure that Congress employed to achieve this purpose. But the approval process set out in section 16 need not be the only mechanism that would be consistent with a market-fostering purpose. This suggests an analogy with the 94th Congress's purposes in enacting the Medical Device Amendments, which included fostering a vulnerable medical device industry. Under a purpose-based analysis, limiting manufacturers' post-market liability is consistent with Congress's broad purposes.

But there are many problems with this argument. One is that the 94th Congress expressly addressed the issue of post-market liability for device manufacturers by including Section 360k in the MDA. This suggests that the earlier Congress may have had a broader purpose in mind when it enacted the MDA than did the later body that enacted the SMDA. Another is that a purpose-based analysis must consider the legislative background—the SMDA, like the MDA, was amending the FDCA. And

320. *See generally* 136 CONG. REC. 36,007 (1990).

321. *See* 136 CONG. REC. 36,007, 36,162 (1990) (comments of Sen. Kennedy) (“[T]he legislation streamlines regulatory review procedures for so-called combination products. . . .”); *id.* at 36,163 (comments of Sen. Dodd) (stating the same); *id.* (comments of Sen. Durenberger) (“I think it is important that we acted to streamline the regulatory barriers facing [combination] products.”).

322. *See id.* at 36,162–36,163.

both Congress and the courts have recognized that a central purpose of the FDCA is to ensure the safety of drugs and devices approved for sale in the U.S. market.³²³ As with a textual and an intent-based analysis, a purpose-based analysis cannot answer the question of whether Congress intended Section 360k to preempt failure-to-warn claims against drug-device combination products manufacturers.

If the relevant identity in a preemption analysis is a combination product's statutory identity, and if Section 360k applies only to products defined as a medical device, the necessary conclusion is that Section 360k does not preempt failure-to-warn claims against the manufacturers of drug-device combination products. But the analysis set out above is more consistent with the limited claim that the scope of Section 360k is ambiguous with respect to combination products. Courts could adopt either interpretation of the language of the express preemption provision.

From the normative position from which this Article proceeds, extending the scope of Section 360k to combination products is undesirable because it subverts the calibrated information-forcing system of medical products regulation outlined in section I.C. The information-forcing account views Section 360k as one of the means used to calibrate manufacturers' obligations to produce and disseminate information about product risk and the burden of producing and disseminating that information. Because device risks can be forecast based on a limited set of factors, a somewhat limited federal layer (PMA, not NDA approval) and preemption of the state layer facilitate the production and dissemination of enough information to ensure safety.³²⁴ But unlike non-combination devices, the risks posed by a drug-device combination cannot be determined by examining a limited set of factors. As discussed earlier, these products present all the unpredictable risks of new drugs, plus qualitative super-additive risks that the scientific community cannot foresee.³²⁵ Thus, the information needed to ensure safety actually exceeds the information needed for a non-combination new drug. Hence, a more robust approach, requiring more, rather than less, information about risk is desirable.

C. Explaining Courts' Decisions in the Combination Products Cases

Courts have assumed the answers to three key questions about the nature of combination products and the scope of Section 360k, two of which have led them to find that failure-to-warn claims against drug-

323. *See supra* note 9.

324. *See supra* section I.C.

325. *See supra* section II.B.

device combination product manufacturers are preempted. Part IV turns to the question of what can be done to narrow the regulatory gap. But first, several potential explanations for courts' preemption decisions should be addressed here. One context-specific explanation is that the focus in the Infuse/LT-Cage cases has not been on these questions. Rather, in the Infuse/LT-Cage product cases, litigants and courts have focused on the fact that nearly 90% of the uses of the product were off-label, and on the argument that Medtronic aggressively (and illegally) promoted this off-label use. Most plaintiffs have assumed that Section 360k would apply to the Infuse/LT-Cage product absent the manufacturer's off-label promotion. Plaintiffs have attempted to avoid preemption by arguing that the off-label promotion vitiates the preemptive effect of Section 360k. Most, but not all, courts have rejected this argument.³²⁶ And the courts that have rejected the off-label argument have gone on to conduct preemption analyses, assuming the answers to the key questions regarding the construction of the statutory term "combination product" and the scope of Section 360k. Thus, the focus on Medtronic's off-label promotion does not explain the Infuse/LT-Cage cases.

The attempts to explain the Supreme Court's recent drug and device preemption holdings described earlier can be applied to the lower courts' holdings in the combination products cases.³²⁷ Many scholars have located doctrinal sources for the Supreme Court's holdings, particularly that the Court has inverted the presumption against preemption into a presumption in favor of preemption.³²⁸ Others have focused on the critical attitudes attributed to certain Justices concerning the effects of tort and product liability law. Still others have described the Court's preemption decisions as a manifestation a pro-business or a deregulatory agenda that some justices seek to implement.³²⁹ These explanations can apply directly to the lower court decisions in the combination products cases. That is, lower court judges may share these doctrinal and policy views. The explanations may also apply indirectly, in that lower court judges

326. See e.g., *Ramirez v. Medtronic Inc.*, 961 F. Supp. 2d 977, 996 (D. Ariz. 2013) (discussing how off-label promotion obviates need for plaintiff to plead a parallel claim).

327. See *supra* notes 163–178 and accompanying text.

328. See Chemerinsky, *supra* note 164, at 1319 ("The only way to make sense of the [*Geier*] case is to see it as putting a presumption in favor of preemption."); Mary J. Davis, *Unmasking the Presumption in Favor of Preemption*, 53 S.C. L. REV. 967, 968 (2002) ("It is inescapable: there is a presumption in favor of preemption."); Gillian E. Metzger, *Federalism and Federal Agency Reform*, 111 COLUM. L. REV. 1, 20 (2011) ("*Watters v. Wachovia Bank* appeared to apply a presumption in favor of preemption.") (emphasis in original).

329. Sharkey, *The Anti-Deference Pro-Preemption Paradox*, *supra* note 174, at 806; see also *id.* at 809 n.14 (listing scholars who have argued that the Roberts Court's decisions embody a pro-business, anti-regulatory agenda).

may rule strategically, recognizing the views of the court or courts above them and aiming to minimize the likelihood of being reversed on appeal.

But the analysis in section III.B suggests that lower courts' preemption findings in the drug-device combination products cases arise from an analytic move antecedent to the preemption analysis itself. The lower courts have been making key assumptions based on their conception of combination products. Assuming that drug-device combination products are medical devices determines the input into the preemption analysis, and as shown above, this determines the output of that analysis. This observation begs the question of *why* courts have routinely made this assumption. The opinions in these cases contain little to nothing that helps to answer this question. This section offers three possible, non-exclusive explanations.

First, litigants have rarely emphasized the distinct nature of combination products, either as products qua products or as legally constructed entities.³³⁰ In most cases courts have heard from both sides that drug-device combination products are devices.

Second, the defendants in these cases have all been medical device manufacturers. A natural assumption—and one that courts could justifiably make over many decades—would be that a product made by a device manufacturer is a device. This is no longer a safe assumption. Companies that had once developed only devices or only drugs are now increasingly creating products that combine devices and drugs. Medtronic, a self-described medical device company,³³¹ markets combination products including drug-eluting stents, steroid-eluting pacemaker and defibrillator leads, implantable drug infusion pumps, and the Infuse/LT-Cage product.³³² Mylan, a self-described pharmaceutical company,³³³ markets combination products including the EpiPen and the

330. See *supra*, notes 279–280 and accompanying text.

331. See *Mission Statement*, MEDTRONIC, <http://www.medtronic.com/us-en/about/mission.html> [<https://perma.cc/CMN3-SMUK>] (stating the company mission is “[t]o contribute to human welfare by application of biomedical engineering in the research, design, manufacture, and sale of instruments or appliances.”).

332. See FDA, PREMARKET APPROVAL (PMA), FDA: U.S. FOOD & DRUG (NOV. 11, 2019), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpMA/pma.cfm?start_search=1&applicant=medtronic&tradename=&productcode=&pmanumber=&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=¢er=D&ivdproducts=off&combinationproducts=on&decisiondatefrom=&decisiondateto=11%2F14%2F2019¬icedatefrom=¬icedateto=&znumber=&pagenum=500 [<https://perma.cc/3XMA-5KKA>] (listing eighteen original PMA approved combination products and over 500 original and PMA supplement approvals for combination products).

333. See *About Us*, MYLAN.COM, <http://www.mylan.com/en/company/about-us> [<https://perma.cc/22QW-DVDM>] (describing product line as “prescription generic, branded generic,

MTFS, a transdermal patch that delivers a generic form of Fentanyl.

The third possible explanation is that combination products and the federal combination products regulatory regime have emerged through a poorly recognized process of incremental evolution. This has been a very different process than the process that created the regulatory regimes for drugs, devices, and biological products. Congress created federal authority over drugs, devices, and biologicals after highly publicized, tragic events caused by one or a few specific products.³³⁴ In effect, widely reported crises led to the creation of regulatory regimes in landmark pieces of legislation. By contrast, the combination products regulatory regime did not emerge out of tragedy. Rather, the regime was created in a largely unnoticed provision of an amendment to an existing regime, in response to industry complaints about premarket burdens. Perhaps the gradual evolution of a distinct product category has eluded recognition.

Two important points hopefully emerge from this Part. First, although there is a tendency to channel combination product approval through the device pathways, this channeling is not a necessary outcome under existing statutes and regulations. Second, although courts have almost all found state tort and products liability claims to be preempted, this is not a necessary outcome under existing statutes, regulations, and Supreme Court precedent. These points suggest that the regulatory gap itself may not be a necessary feature of combination products regulation.

IV. NARROWING THE REGULATORY GAP

The normative position this Article takes is that a layered, calibrated system of information obligations strikes a desirable balance between assuring medical product safety and permitting innovation and timely access. From this position, drug-device combination products, which present the unforeseeable risks of new drugs and the qualitative synergistic risks of drug-device interactions, should be regulated by the most rigorous, two-layered approach—the federal NDA premarket evaluation process and state law post-market failure-to-warn liability. But both the federal and the state sides of this regulatory scheme now function in a truncated fashion. Sections IV.A and IV.B explore the available means by which the federal and state sides of the gap may be narrowed. In effect, this Part tests the proposition that the emergent regulatory system for medical products can survive the challenge presented by combination products.

brand-name . . . drugs, as well as over-the-counter (OTC) remedies”).

334. Paradise et al., *supra* note 66, at 614.

A. Narrowing the Federal Side of the Gap: The FDA's Options

Part III reached the conclusion that channeling combination product premarket approval through the device pathways is not a necessary outcome under existing statutes and regulations. In fact, the FDA retains sufficient statutory authority under which it could narrow, but not completely close, the regulatory gap. First, the FDA could ensure robust risk information production by assigning more drug-device combination products the regulatory identity of a drug. The SMDA vested the authority to assign the regulatory identity of combination products to the Secretary of HHS, who delegates this authority to the FDA.³³⁵ The SMDA also contained a rule of decision for making this assignment, the primary mode of action test.³³⁶ In determining the primary mode of action, the FDA must “evaluat[e] scientific data within its technical expertise,” a classic exercise of discretion by an expert agency to which courts typically defer.³³⁷ Thus, the agency could, in effect, re-channel combination product approvals into the drug pathways.

This might appear to run counter to the SMDA, given that the Act created a rule (the primary mode of action) for assigning regulatory identity that makes it easier for the FDA to assign a device identity.³³⁸ But the legislative history suggests that Section 16 was intended to ease manufacturers' burdens by requiring only a single approval process for any given combination product, not to channel the specific approval process into any specific pathway. Requiring the FDA to assign a regulatory identity based on the primary mode of action arguably serves merely to prevent every drug-device combination product from being regulated as a drug (as would occur were the Agency to use the earlier test based on the achievement of intended effects through *any* drug action). Where the primary mode of action is at all unclear, the FDA could assign combination products to CDER for regulation under the agency's more rigorous drug authorities.

Second, the FDA could improve the information-generating function of the PMA process by requiring more rigorous pivotal study design, for example by insisting on larger sample sizes, blinding of subjects and investigators, the use of sham interventions for the control group, and

335. Pub. L. No. 101-62, § 16, 104 Stat. 4511, 4526 (1990) (codified at 21 U.S.C. § 353(g) (2012)).

336. *Id.*

337. *Prevor v. FDA*, 895 F. Supp. 2d 90, 98 (D.D.C. 2012) (quoting *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996)).

338. *See supra* notes 244–253 and accompanying text.

randomized assignment to treatment or control groups.³³⁹ These changes have been suggested for non-combination high-risk devices by medical scholars. In the combination products context, these steps could improve the quantity and quality of information available to regulators, prescribers, and patients.

However, a number of considerations ultimately limit the utility of these approaches. Although the FDA has discretion in making its determination of the primary mode of action and although this type of determination typically receives *Chevron* deference, in at least one line of recent cases a court has given the Agency's assignment of a regulatory identity a very hard look.³⁴⁰ Given the stakes of this assignment for the manufacturer, it would not be surprising if FDA assignments of a drug regulatory identity to combination products were frequently and vigorously challenged. The *Prevor* cases suggest that courts might seek to constrain the FDA's latitude in making regulatory identity assignments.

The FDA's ability to require more robust clinical data is also limited. Although blinded, randomized, controlled trials have traditionally been regarded as the gold standard, for many device-containing products it is difficult to design a trial with a true control arm. Consider the Infuse/TL-Cage product. At the time the manufacturer sought approval there was a surgically-implanted alternative which could serve as the control. Absent that alternative, a truly blinded, controlled trial might have required a control arm whose subjects underwent a sham surgery. Performing sham interventions in clinical trials has traditionally been considered unethical.³⁴¹ And even if this ethical limitation could be overcome, enrolling subjects in a study using sham interventions would be difficult. Further, increasing sample size may not be possible because many products that include a medical device are used in far fewer patients than are drugs.³⁴²

Thus, attempts to address the regulatory gap through administrative-level efforts can, at best, marginally narrow the gap. The very nature of drug-device combination products leads to the conclusion that they will reach the market with a more limited quantum of risk information than non-combination new drugs. This leaves state failure-to-warn actions as

339. See *supra* notes 74–79 and accompanying text for a discussion of the less rigorous nature of the PMA process.

340. See *Prevor*, 895 F. Supp. 2d at 97 (applying “a thorough, probing, in-depth review” to find that FDA had failed to articulate the reasons for its assignment); *Prevor v. FDA (Prevor II)*, 67 F. Supp. 3d 125, 137 (D.D.C. 2014) (reciting the *Chevron* standard while rejecting FDA's determination of primary mode of action).

341. See Dhruva et al., *supra* note 62 and accompanying text.

342. See *id.*

the remaining mechanism through which the information deficit created by approving new drugs through the PMA pathway might be narrowed.

B. Narrowing the State Side of the Gap: The Miller v. Mylan, Inc. Approach

Part III also drew the conclusion that the preemption of all state tort and products liability claims against the manufacturers of drug-device combination products is not a necessary outcome under existing statutes, regulations, and Supreme Court precedent. The Sixth Circuit’s decision in *Miller v. Mylan, Inc.*³⁴³ provides a paradigm for an alternative approach to the preemption analysis in these cases. *Miller* required courts to interpret the scope of a state statute that functions analogously to section 360k by expressly shielding the manufacturers of certain drugs from liability under state tort and products liability law. The case involved Mylan’s “MFTS” product, a generic version of the fentanyl transdermal patch which is designed to provide a slow and steady infusion of the potent analgesic fentanyl through the skin. The FDA classifies transdermal patches as combination products and assigns regulatory responsibility to CDER, which uses drug and device authorities “as necessary.”³⁴⁴

Miller arose after Beth Ann Kelly died as the result of a Mylan MFTS malfunction, which led to the delivery of a dose of fentanyl several-fold greater than the therapeutic dose. Kelly’s estate sued the manufacturer under a variety of state law theories. Mylan moved for dismissal under section 600.2946(5),³⁴⁵ a Michigan statute that provides that “a product that is a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the [FDA], and the drug and its labeling were in compliance with the [FDA]’s approval.”³⁴⁶

The district court found that Mylan’s product was a drug, based on the FDA’s assignment of a regulatory identity: “[t]here is no question that in considering Mylan’s ANDA, the FDA deemed the MFTS, the patch, to be a drug; not a device and not something less than its whole.”³⁴⁷ The court

343. *Miller v. Mylan, Inc. (Miller II)*, 741 F.3d 674 (6th Cir. 2014).

344. *Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health*, FDA (2018), <https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121177.htm> [<https://perma.cc/36YT-3XR5>].

345. *Miller II*, 741 F.3d at 677.

346. Mich. Comp. Laws § 600.2946(5) (2019).

347. *Miller v. Mylan Inc. (Miller I)*, No. 12-11684, 2012 WL 5300721, at *6 (E.D. Mich. Oct. 25, 2012), *rev’d*, 741 F.3d 674 (6th Cir. 2014).

held that section 600.2946(5), coupled with Mylan's compliance with FDA-imposed requirements, provided Mylan with immunity.

The Sixth Circuit reversed in a split decision.³⁴⁸ All three members of the panel agreed that under federal statute and FDA regulation, "combination product" is a distinct product category.³⁴⁹ The majority explained that the Safe Medical Devices Act had "create[d] a distinction between how a product is *defined* and how that product will be *regulated*."³⁵⁰ The majority found that under the FDCA, the fentanyl patch is statutorily defined as a combination product, and that FDA regulates the combination product as a drug.³⁵¹ The dissent accepted the majority's distinction between statutory definition and regulatory identity, but disagreed with the conclusion that MFTS fits the statutory definition of a combination product.³⁵² Thus, all three members of the panel parted ways with the majority of courts in the Infuse/LT-Cage, drug-eluting stent, and other combination products cases, recognizing that combination products are not, as a matter of statutory definition, drugs or devices. Rather, the Sixth Circuit recognized that combination products must be conceived of as *sui generis* entities.

The majority construed the Michigan statute as conferring immunity only on the manufacturers of products statutorily defined as "drugs," but not on the manufacturers of products statutorily defined as "combination products."³⁵³ The majority rejected Mylan's argument that the FDA's assignment of a regulatory identity was the relevant consideration. To the majority, the relevant consideration for determining whether a state statute shielding the manufacturer of a drug from state common law liability was the product's statutory definition.³⁵⁴

Miller is germane to the combination products cases. The facts in these cases are analogous: plaintiffs brought failure-to-warn claims for injuries caused by a product the FDA found to meet that statutory definition of a combination product. And the statutes on which the defendants relied, Michigan's section 600.2946(5) and Congress's 21 U.S.C. § 360k(a), are cast in analogous terms, except that the Michigan provision refers to "a product that is a drug," while the federal provision refers "to a device."

348. *Miller II*, 741 F.3d at 675.

349. *Id.* at 677, 681.

350. *Id.* at 677.

351. *Id.*

352. *Id.* at 681 (McKeague, J., dissenting) ("I turn to those [federal drug, device, and combination product] definitions to see if Mylan's Fentanyl Transdermal System is a combination product.").

353. *Id.* at 677–678 (majority opinion).

354. *Id.* at 677.

The *Miller* Court explicitly addressed the questions most other courts have overlooked. *Miller*'s key analytic moves—recognizing that “combination products” are a distinct product category and that statutory language extending the scope of coverage to a medical product category refers to the product’s statutory definition, not the regulatory identity—provide answers to the questions identified in section III.B. These answers would lead courts to different preemption outcomes than most have reached. Under the *Miller* approach, Section 360k, by its terms, applies solely to “devices,”³⁵⁵ and not to products regulated as devices. The FDA’s interpretation of Section 360k, by the terms of the implementing regulation, likewise applies solely to devices.³⁵⁶ Under the reasoning in *Miller*, combination products, regardless of how they are regulated, are not devices, and so the express preemption provision, section 360k, would not apply.

As yet, no court has adopted the *Miller* approach in a federal preemption analysis involving a combination product. But the Sixth Circuit’s analysis casts an important light on those cases. A few other courts have used similar reasoning. One early combination products case involved a prosthetic heart valve (a device) that incorporated an antibacterial coating of silver (a drug).³⁵⁷ Patients who received this valve had an elevated risk of developing a failure of the connection between the valve and the heart, which can lead to life-threatening complications.³⁵⁸ The plaintiffs asserted that the valve was a drug-device combination product, and thus, that the express preemption provision of the MDA should not apply.³⁵⁹ To the Minnesota District Court, the product’s statutory definition was crucial: “the express preemption principles and case law . . . do not apply to combination products or to drugs.”³⁶⁰ And in a patent term extension case under Section 156 of the Hatch-Waxman Act, the Eastern District of Virginia rejected the PTO’s finding that a drug

355. 21 U.S.C. § 360k(a) (2012) (“[N]o State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—(1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and (2) which relates to the safety or effectiveness of the device. . .”).

356. 21 C.F.R. § 808.1(d) (2019) (“State or local requirements are preempted only when the Food and Drug Administration has established specific counterpart regulations . . . applicable to a particular device under the act. . .”).

357. *In re St. Jude Med., Inc. Silzone Heart Valves Prod. Liab. Litig.*, No. MDL 01–1396 JRTFLN, 2004 WL 45503, at *1 (D. Minn. Jan. 5, 2004), *rev’d* 425 F.3d 1116 (8th Cir. 2005).

358. *Id.*

359. *Id.* at *14. The FDA does not consider the Silzone to be a combination product, but rather a Class III medical device. *Id.* at *3.

360. *Id.*

eluting stent (the Zilver PTX) was a medical device simply because the FDA regulated it as such.³⁶¹ Rather “the FDA’s determination of a primary mode of action is merely an identification of the predominate means by which the product achieves its therapeutic effect,” establishing only the regulatory identity.³⁶²

The *Miller* approach appears to be permissible under existing statutes and FDA regulations. Thus, courts have the means at their disposal to narrow the regulatory gap they have helped to create. Courts could adopt the *Miller* court’s approach to Section 360k and find that the express preemption language there does not apply to combination products. But the utility of this approach is also limited. Courts would still need to address the application of implied preemption principles in these cases.³⁶³ Here, the question would be which approach to implied preemption courts would take. One possibility is that state failure-to-warn actions would not fit through the narrow statutory gap created by *Riegel* and *Buckman*.³⁶⁴ State tort and products liability verdicts would require the manufacturer to change the product label that the FDA requires, creating an apparent conflict. But FDA regulations contain a route through which the manufacturer of a PMA-approved device can change its labeling in response to new safety information,³⁶⁵ analogous to the CBE provisions at issue in *Wyeth*.³⁶⁶ Thus, manufacturers could comply with both federal and state labeling requirements, suggesting that courts would find state tort and products liability actions against combination products regulated as devices not to be impliedly preempted. Alternatively, *Riegel* and *Buckman*, which concerned products statutorily defined as devices, might not apply to cases involving products statutorily defined as combination products. Courts might well need to return to first principles, defining an implied preemption rule for combination products based on their interpretation of Congress’s preemptive intent.

None of these suggestions can completely close the regulatory gap for high-risk device-new drug combination products. Because of the practical and ethical limitations discussed in section IV.A, these products will inevitably reach the market with a lesser quantum of risk information than

361. *Angiotech Pharm. Inc. v. Lee*, 191 F. Supp. 3d 509, 524 (E.D. Va. 2016).

362. *Id.*

363. *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 871 (2000) (stating that implied preemption principles apply even where an express preemption provision is present).

364. *Id.* at 868.

365. 21 C.F.R. § 814.39(d)(1) (2019).

366. *See supra* section I.A. Because the express preemption provision has allowed courts to dispose of cases, this provision has not litigated.

non-combination new drugs or high-risk devices by themselves. And because of the sweeping, implied preemption rule established by *Buckman*,³⁶⁷ adopting the *Miller* approach would not necessarily allow state failure-to-warn claims to proceed. Further, because state common law actions are sub-optimal information-forcing mechanisms,³⁶⁸ post-market liability would at best serve a function that may be described as too-little-too-late. What this indicates is that, by themselves, the suggestions offered in this Part are not sufficient to close the regulatory gap. Because the deficit in knowledge about drug-device combination product risk arises in large part from unforeseeable qualitative risks, the gap is a consequence of combination products themselves. If the gap is to be closed, it is incumbent on the scientific community to develop the means to monitor for and ultimately to predict these risks.

V. VIEWING MEDICAL PRODUCT REGULATION AS AN EMERGENT SYSTEM: UTILITY AND LIMITATIONS

The analysis of the combination products cases just presented is premised on the view of medical products regulation through FDA approval and state common law as a coherent, calibrated system of information-producing duties that emerges from the functioning of several independent regulatory inputs. This view differs from the common view of FDA premarket approval and state post-market tort and products liability law as inherently conflicting systems. This Part describes a number of advantages of this approach, and assess two significant criticisms.

Critical to this Article is the recognition that a regulatory system can achieve certain effects through the function of many independent regulatory subsystems, each of which seeks to achieve other sets of policy objectives. In the medical product context, the NDA, ANDA, PMA, and Section 510(k) premarket processes all embody different balances of partially overlapping sets of policies.³⁶⁹ State tort and product liability law embodies yet other policy balances. And the Supreme Court's preemption decisions explicitly recognized yet other considerations.³⁷⁰ The relative priority assigned to incentivizing the generation and dissemination of risk information varies widely across these regulatory subsystems. But the overall system that emerges from these subsystems prioritizes the imposition of a calibrated system of information obligations on medical product manufacturers.

367. *See supra* notes 125–129 and accompanying text.

368. *See supra* notes 148–157 and accompanying text.

369. *See supra* section I.A.

370. *See supra* sections I.B, I.D.

In isolation, the Supreme Court's preemption decisions in *Wyeth* and *PLIVA* appear to create bizarre outcomes.³⁷¹ Yet when viewed as parts of a system that calibrates information-generating obligations to information deficits, these decisions take on very different valence—they make sense. The converse is also true. Viewing federal and state regulation of medical products as an emergent system can make evident how decisions that are seemingly consistent with the existing regulatory structure actually deviate from, or even subvert, that structure. In the cases involving combination products, the lower federal and state courts have cast their preemption decisions as aligning comfortably with existing preemption jurisprudence.³⁷² Indeed, if drug-device combination products are devices, or if Section 360k applies to all products regulated as devices, the majority approach does align with the existing case law. But from the perspective adopted here, preemption decisions that eliminate the state-based second layer of information-forcing are inconsistent with the function of the more-broadly conceived regulatory system. This inconsistency led to the recognition that courts' preemption analyses have been reliant on certain key, unwarranted assumptions.

Another benefit is that this approach shifts the focus toward perspectives more closely aligned with those of the regulated entities and with others who are impacted by the totality of the regulatory inputs. In the medical products context, device and pharma companies considering whether to embark on development projects may make decisions based on the totality of their information-producing obligations and their anticipated costs and risks. Prescribers and patients may select products based on the totality of information available about risk and benefit. Each individual subsystem at each level of regulation contributes only a portion of the manufacturer's obligations and risks and of the information that is available. But to the product developers and users, the totality of the information is key.

A third benefit is that conceiving of a regulatory system as the emergent result of multiple subsystems is that this conception makes clear how small changes to any part of any of the subsystems can impact the effects of the overall system. If, as I have just argued, recent preemption decisions in drug-device combination products cases represent a change, the effects of that change extend far beyond drug-eluting stents and spinal fusion products. As combination products come to account for a strong plurality of all medical products, removing the state layer of information forcing

371. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 625 (2011) (“We recognize that from the [plaintiffs’] perspective . . . finding pre-emption here but not in *Wyeth* makes little sense.”); *id.* at 643 (Sotomayor, J., dissenting) (arguing that the “decision leads to so many absurd consequences. . . .”).

372. See *supra* notes 281–284 and accompanying text.

from this large category of products for which risk is inherently unpredictable will make it impossible to view medical product regulation as a coherent system of calibrated information-forcing obligations. In effect, a new regulatory system may be emerging. This in turn points out how fragile regulatory systems can be. If small changes to any one piece of the system can disrupt the normatively desirable functions of that system, continuity is unlikely.

One important criticism that may be leveled at this Article is that the exercise of finding emergent regulatory systems is too malleable to be of much significance. Simply by manipulating the scope of the regulated entity, and by arbitrarily selecting regulatory goals and regulatory inputs, one can find an emergent system almost anywhere. The analysis presented in this Article attempts to avoid this danger. The choice of the scope of the regulated entity was not overinclusive. Defining the regulated entity to consist of the manufacturers of prescription drugs, medical devices, and biologics is consistent with most scholarly accounts of medical product regulation. These accounts typically exclude other FDA-regulated products such as food and cosmetics, and other consumer products that may impact health. Nor was the choice of scope underinclusive. The topic—combination medical products—suggests that the barriers between drugs, devices, and biologics, and between their manufacturers, are rapidly breaking down.³⁷³ And scholarly commentary has indicated that the regulation of these products should no longer be conducted in separate silos.³⁷⁴

The choice of regulatory goal is more open to challenge. My prioritization of ensuring medical product safety is, of course, a normative one, to which my past as a clinician predisposes. Some members of the medical products industry have maintained that the purpose of regulation is to ensure a well-functioning marketplace of new and innovative products. The Supreme Court has, in recent decisions, echoed this view. As noted above, though, many of the significant pieces of legislation that form the federal regulatory regime cite the goal of ensuring that medical products are safe. Several landmark pieces of legislation, including the Biologics Control Act, the FDCA, and the MDA arose out of highly publicized catastrophes involving medical products.³⁷⁵ And state tort and products liability law have long been seen as part of the states' police power to ensure safety and wellbeing.

373. See *supra* notes 331–333 and accompanying text.

374. See, e.g., Foote & Berlin, *supra* note 4, at 641–44.

375. See generally *id.*

Finally, my choice of regulatory inputs is consistent with the existing scholarly literature, which focuses on FDA approval and state tort and products liability law.³⁷⁶ However, there is an under-inclusiveness problem that must be recognized here. Information-forcing comes from many sources, not just from federal premarket evaluation and state post-market tort and products liability law. The FDA can require manufacturers, in certain contexts, to conduct post-market studies to ensure safety. The FDCA contains many reporting requirements. Medical researchers perform studies of drugs, devices, and biologics, and often uncover new information about risk.³⁷⁷ And patient and consumer networks, greatly aided by the connectedness afforded by social media, can aggregate isolated adverse events and bring problems to light.³⁷⁸ Every one of these can be seen as a form of regulation, in that they may incentivize manufacturers to somehow change their behavior. The challenge is to construct a model with a manageable number of inputs.

A second potential criticism is that the emergent system that section I.C describes is less well-calibrated than I have indicated. section I.C has already addressed the limitations of state tort and products liability law as information-forcing systems.³⁷⁹ Another weakness is centered on the regulation of intermediate-risk devices. The Section 510(k) notification process does not require the production of clinical data about risk. And in many circuits, state failure-to-warn claims are very likely to be preempted. Thus, the information deficit about risk appears to be untouched by the emergent regulatory system. One important point to recall, though, is that under the mid-twentieth century understanding of medical devices that the system embodies, device risks in general were predictable in advance of any clinical testing, and the risks of Class II devices were more predictable than those of Class III devices.

CONCLUSION

A functional account of the regulation of traditional medical products, including federal and state regulation of prescription drugs and medical devices, describes an emergent, calibrated mechanism that incentivizes manufacturers to generate and disclose the optimal amount of information

376. See, e.g., Sharkey, *States Versus ADA*, *supra* note 10 at 1610.

377. See generally Carragee, Hurwitz & Weiner, *supra* note 228 (reviewing post-market clinical trials that revealed the complication rates associated with the Infuse/LT-Cage product).

378. Diane Bloom et al., *The Rules of Engagement: CTTI Recommendations for Successful Collaborations Between Sponsors and Patient Groups Around Clinical Trials*, 52 *THERAPEUTIC & REG. SCI.* 208, 208 (2018) (discussing role of patient groups in monitoring drug safety).

379. See *supra*, notes 148–157.

about product risk. The amount of information required is based on the ability to predict the risks that a product presents and the burdens that information production and dissemination impose. But a new and rapidly growing product category—combination products—threatens to upend this calibrated information-forcing system. Drug-device combination products may pose risks that are more difficult to predict than the risks of any other product category. But the manufacturer of a new drug can avoid the rigorous and costly NDA process by submitting the new drug as a constituent of a combination product, which may be approved through the less-rigorous device pathway. And, under many recent lower court decisions, the manufacturer will be shielded from state failure-to-warn claims. The regulatory gap that results causes hundreds of thousands of Americans, or more, to be exposed to new drugs, the risks of which are not understood to the same extent as are the risks posed by other new drugs. Both the FDA and the courts have the means to narrow—but not to completely eliminate—the regulatory gap.