

EPIPEN, PATENTS, AND LIFE AND DEATH

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Drug pricing disputes, while significant public health concerns, are not typically immediate life or death matters. But they may be for certain emergency medicines, medicines used for potentially lethal and rapidly onset illnesses or injuries. This is especially true for emergency drug-device combination products, like Mylan's EpiPen, for which patients can bear a significant brunt of the products' cost. Scholarly commentary on the controversy surrounding the pricing of Mylan's EpiPen, however, has largely elided over this relationship among combination products, emergency medicine, and patient payment, often focusing instead on classic issues of antitrust and competition. This brief Essay explores how EpiPen's pricing capacity is a function of a peculiar intersection of emergency medicine, FDA law and policy, and patents, and suggests areas of further analysis for other drug-device emergency combination products.

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INTRODUCTION

Drug-pricing disputes, while significant policy and public health concerns, do not typically present immediate life or death consequences. But drugs for emergency medicine—that is, drugs for “unforeseen illness or injury . . . requiring expeditious medical, surgical, or psychiatric care”¹—may be exceptions.² Because access to drugs often depends on competitive pricing, drug manufacturers’ control of pricing levers, such as patents, has the power to save—or threaten—the lives of patients in critical danger.³ This is exacerbated where patients need drug-device combination products for self-administration in extreme situations, as is the case for Mylan’s emergency epinephrine autoinjector, EpiPen.⁴ In the words of one pharmacist, the price of an EpiPen “could mean life or death.”⁵

At the same time, EpiPen, specifically, has a complex legal and regulatory history that belies a simple connection between competitive pricing and access to emergency medicines. While scholarship and reporting have largely focused on the ways classically anticompetitive conduct has arguably enabled EpiPen’s pricing,⁶ it

¹ DEFINITION OF EMERGENCY MEDICINE, AM. COLL. OF EMERGENCY PHYSICIANS (2021), <https://www.acep.org/patient-care/policy-statements/definition-of-emergency-medicine> [<https://perma.cc/QMB2-4RD4>].

² Insulin may also be an example where drug pricing can lead to near immediate life-or-death consequences for patients. See generally S. Vincent Rajkumar, *The High Cost of Insulin in the United States: An Urgent Call to Action*, 95 MAYO CLINIC PROC. 22 (2020) (describing the reasons for, and risks of, the high cost of insulin in the United States); Colleen V. Chien, *Cheap Drugs at What Price to Innovation: Does the Compulsory Licensing of Pharmaceuticals Hurt Innovation?*, 18 BERK. TECH. L.J. 853, 888 (2003) (describing pricing controversies over insulin). Nonetheless, insulin may itself be a special case in that it is used *both* in a daily regime *and* as an emergency medicine. See generally Ziv Harel & Kamel S. Kamel, *Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalemia: A Systematic Review*, PLOS ONE, May 2016.

³ See Govind Persad, *Examining Pharmaceutical Exceptionalism: Intellectual Property, Practical Expediency, and Global Health*, 18 YALE J. HEALTH POL’Y L. & ETHICS 157, 159 (2019) (“Pharmaceutical exceptionalists regard IP rights in medicines as a major impediment to global health, and therefore argue for eliminating IP protections or imposing greater obligations on IP holders.”); Rebecca E. Woltz, *A Corporate Duty to Rescue: Biopharmaceutical Companies and Access to Medications*, 94 IND. L.J. 1163, 1165 (2019) (noting the same for “life-saving medications”).

⁴ See, e.g., EPIPEN PRESCRIBING INFORMATION (Dec. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/019430s0911b1.pdf [<https://perma.cc/2TYM-8D5M>] (describing the use of EpiPen in emergencies).

⁵ *Cost of EpiPen Continues to Rise Putting Burden on People with Allergies*, WKYT (Aug. 17, 2016), <https://www.wkyt.com/content/news/Cost-of-EpiPen-continues-to-rise--390412751.html> [<https://perma.cc/D7H4-PQ36>].

⁶ See, e.g., Michael A. Carrier, Mark A. Lemley & Shawn Miller, *Playing Both Sides? Branded Sales, Generic Drugs, and Antitrust Policy*, 71 HASTINGS L.J. 307 (2020); Ramsi A. Woodcock, *The Antitrust Duty to Charge Low Prices*, 39 CARDOZO L. REV. 1741 (2018); Michael A. Carrier & Carl J. Minniti III, *The Untold EpiPen Story: How Mylan Hiked Prices by Blocking Rivals*, 102 CORNELL L. REV. ONLINE 53 (2017); Ed Silverman & Ike Swetlitz, *Sanofi Sues Mylan*

is also critical to consider how the intersection of patent and FDA law has given rise to EpiPen's dominant market position. Although the EpiPen story is in many ways atypical, if not unique, understanding the connections among emergency medicine, the regulation of drug-device combination products, and patent protection may be instructive in assessing—and possibly preventing—pricing controversies for other emergency medicine products.

This brief Essay examines these connections in the context of EpiPen and focuses, in particular, on the intellectual property and regulatory regimes that helped Mylan maintain high prices and depress competition for EpiPen. It concludes by highlighting several areas for policymakers and regulators to watch as drug-device emergency medicine combination products, and autoinjectors more generally, become increasingly popular.⁷

I

EPIPEN'S MARKET POSITION

Certain emergency medicines, which lay people may need to administer during an emergency before trained medical personnel can arrive, come in pre-filled, self-injectable syringes, also known as “autoinjectors.”⁸ This is true of Mylan's EpiPen, which is a ready-to-use, pre-filled, self-administered syringe containing epinephrine, a drug that treats life-threatening allergic reactions.⁹ Children and adults with severe nut allergies, for example, often carry epinephrine autoinjectors to halt runaway allergic reactions in case they come into contact with the allergen.¹⁰ Upon experiencing the initial symptoms of anaphylactic shock—a life-threatening allergic reaction—the person would immediately use the preloaded autoinjector to inject themselves with epinephrine.¹¹ Modern epinephrine autoinjectors are critical for health—for example, one study of roughly six thousand schools found that eleven percent reported having one or more anaphylactic events during a single school

Over Alleged Anti-Competitive Marketing of EpiPen, STAT NEWS (Apr. 24, 2017), <https://www.statnews.com/pharmalot/2017/04/24/sanofi-mylan-antitrust> [<https://perma.cc/6828-NU7L>].

⁷ This would include drug-device combination products that allow layperson-administration of naloxone, a drug for reversing opioid overdose, and those products, similarly have been subject to pricing controversies. *See, e.g.*, Ravi Gupta, Nilay D. Shah & Joseph S. Ross, *The Rising Price of Naloxone—Risks to Efforts to Stem Overdose Deaths*, 375 NEW ENGL. J. MED. 2213 (2016); *see also* Cindy H. Dubin, *Injection Devices: Will COVID-19 Deliver Growth to the Market?*, DRUG DEV. & DELIVERY, Sept. 2020, at 46 (describing increasing pharmaceutical industry interest in developing autoinjector products).

⁸ *See* Dubin, *supra* note 7, at 46. Drugs intended for chronic and other non-emergency conditions might also be sold as autoinjectors for various reasons. *See id.*

⁹ EPIPEN PRESCRIBING INFORMATION, *supra* note 4.

¹⁰ *See Peanut Allergy*, MAYO CLINIC, <https://www.mayoclinic.org/diseases-conditions/peanut-allergy/symptoms-causes/syc-20376175> [<https://perma.cc/3QKX-N98U>] (last visited May 27, 2021).

¹¹ HIGHLIGHTS OF PRESCRIBING INFORMATION, *supra* note 4.

year.¹² The benefits of epinephrine autoinjectors have recently led both states and the federal government to address their availability and use in schools.¹³

But the concept of rapidly deploying epinephrine to treat anaphylaxis is not new. Indeed, EpiPen's roots can be traced back to a roughly century-old drug, epinephrine,¹⁴ administered using a 360-year-old technology, the hypodermic needle.¹⁵ But EpiPen's easy-to-use design and familiarity to consumers, combined with increased public awareness of severe allergic conditions, have allowed Mylan to recently—and rapidly—profit from this long-standing medical knowledge. After a wildly successful marketing and public awareness campaign, Mylan captured 95% of the epinephrine autoinjector market.¹⁶ For various reasons, patients often pay significant out-of-pocket costs for EpiPens,¹⁷ although Mylan offers rebates for some of these purchases.¹⁸

EpiPen's popularity has much to do with Mylan's own efforts. Beginning with Heather Bresch's tenure at Mylan, first as its Director of Government Relations and then as its CEO starting in 2012, the company has embarked on a wide-ranging public awareness campaign about anaphylaxis and EpiPens' role in saving lives.¹⁹ This has included pairing with celebrities, such as Sarah Jessica Parker (who later

¹² Susan L. Hogue, Diana Goss, Kelly Hollis, Suyapa Silvia & Martha V. White, *Training and Administration of Epinephrine Auto-Injectors for Anaphylaxis Treatment in US Schools: Results from the EpiPen4Schools® Pilot Survey*, 9 J. ASTHMA & ALLERGY 109, 110 (2016).

¹³ 42 U.S.C. § 280g(d); see also Ashley Noble, *Increasing Access to Epinephrine*, NAT'L CONF. OF STATE LEGISLATURES (2016) (describing the state and federal laws).

¹⁴ See Walter Sneader, *The Discovery and Synthesis of Epinephrine*, 14 DRUG NEWS & PERSPS. 491, 492 (2001).

¹⁵ See C. Ball, *The Early Development of Intravenous Apparatus*, 34 ANAESTHESIA & INTENSIVE CARE 22, 22 (2006) (dating the first modern intravenous needle to Christopher Wren's experiments in 1656).

¹⁶ Jen Wiczner, *Mylan CEO Blamed Obamacare for EpiPen Sticker Shock*, FORTUNE (Aug. 24, 2016), <http://fortune.com/2016/08/24/mylan-ceo-epipen-heather-bresch> [<https://perma.cc/784H-9TRZ>].

¹⁷ While epinephrine autoinjectors are covered by many health insurance programs, the timing and necessary quantity of such purchases may not be fully covered in all circumstances, thus requiring the patient to bear the brunt of any out-of-pocket costs. Cf. Michelle M. Mello, *What Makes Ensuring Access to Affordable Prescription Drugs the Hardest Problem in Health Policy?*, 102 MINN. L. REV. 2273, 2275 (2018) (describing out-of-pocket costs for EpiPen and a competitor product, Auvi-Q). One of the authors (PJZ) also can attest to this from personal experience.

¹⁸ See *Access and Savings Program*, EPIPEN, <https://www.epipen.com/paying-for-epipen-and-generic> [<https://perma.cc/5N7B-APAG>] (last visited May 27, 2021) (describing EpiPen's savings programs); see also Mello, *supra* note 17, at 2275 (describing kaléo's "zero-cost prescription" for its epinephrine autoinjector, Auvi-Q, and pharmaceutical companies' financial incentives to offer such programs); Wolitz, *supra* note 3, at 1199–200 (explaining pharmaceutical companies' financial incentives to offer patient assistance programs).

¹⁹ See Cynthia Koons & Robert Langreth, *How Marketing Turned the EpiPen Into a Billion-Dollar Business*, BLOOMBERG NEWS (Sept. 23, 2015), <https://www.bloomberg.com/news/articles/2015-09-23/how-marketing-turned-the-epipen-into-a-billion-dollar-business> [<https://perma.cc/2RJE-Q7BD>].

withdrew from the relationship).²⁰ Indeed, Mylan's EpiPen has become such a cultural phenomenon that the term "EpiPen" is now often used to refer to epinephrine autoinjectors of all sorts, whether Mylan's or one of its competitors.²¹

Beyond this broad promotional campaign, Mylan also has used legal and regulatory mechanisms to apparently keep competitors at bay. One important example of these efforts is Mylan's work to make EpiPen the exclusive supply of epinephrine autoinjectors in school infirmaries through its "EpiPen4Schools" program. A 2016 report from *STAT News* documented that the program offered increased rebates to schools that purchased EpiPens if they signed what was effectively an exclusive supply agreement.²² And Mylan offered state Medicaid programs larger rebates if they eased EpiPens' prescription rules relative to competitors.²³ As another example, Mylan engineered several patent litigation settlements with competitors that delayed market entry for competing products.²⁴ Taken together, such efforts yielded EpiPen a dominant—if potentially anticompetitive—market position.²⁵

From 2007 to 2016, to great controversy, Mylan capitalized on this market position by raising the wholesale price of an EpiPen autoinjector two-pack from around \$100 to \$600—a roughly 500% increase.²⁶ Because of EpiPens' potential to literally save lives—in particular, the lives of children—the price increase sparked public outrage, including complaints that Mylan engaged in "price gouging."²⁷ The House Committee on Oversight and Government Reform held a hearing on the matter and Bresch, herself, was called to testify.²⁸ Bresch's testimony did little to extinguish the public ire focused on Mylan, and the CEO was rebuked by

²⁰ Rebecca Robbins, *Sarah Jessica Parker Cuts Ties with Mylan in Anger over EpiPen Price Hikes*, STAT NEWS (Aug. 25, 2016), <https://www.statnews.com/2016/08/25/sarah-jessica-parker-epipen> [https://perma.cc/53FC-PRXK].

²¹ See Mike Mireles, *My My Mylan: The Trademark Silver Lining for Mylan's EPIPEN*, IPKAT (Sept. 2, 2016), <https://ipkitten.blogspot.com/2016/09/my-my-mylan-trademark-silver-lining-for.html> [https://perma.cc/KH3Q-RPTV] (discussing these issues in the trademark context).

²² See Ike Swetlitz & Ed Silverman, *Mylan May Have Violated Antitrust Law in Its EpiPen Sales to Schools, Legal Experts Say*, STAT NEWS (Aug. 25, 2016), <https://www.statnews.com/2016/08/25/mylan-antitrust-epipen-schools> [https://perma.cc/98YP-89CU] (noting Mylan required schools to "not in the next twelve (12) months purchase any products that are competitive to EpiPen® Auto-Injectors").

²³ Ike Swetlitz, *Mylan Offered EpiPen Discounts to States in Exchange for Privileged Status, Documents Show*, STAT NEWS (June 22, 2017), <https://www.statnews.com/2017/06/22/mylan-epipen-discount-medicare-preferred> [https://perma.cc/7YHT-DKC6].

²⁴ Carrier & Minniti, *supra* note 6, at 59–64.

²⁵ See *id.* at 59 (noting Mylan's efforts make it difficult to compete and "effectively restrain EpiPen pricing").

²⁶ See Mello, *supra* note 17, at 2274.

²⁷ Editorial, *The EpiPen Outrage Continues*, N.Y. TIMES (Sept. 21, 2016), <http://www.nytimes.com/2016/09/22/opinion/the-epipen-outrage-continues.html> [https://perma.cc/7CKJ-SKMJ].

²⁸ See, e.g., Mello, *supra* note 17, at 2275.

shareholders in a compensation vote the following year.²⁹

Mylan has since attempted to quell the controversy by offering its own authorized generic version of EpiPen—at \$300 a two-pack.³⁰ It has not, however, significantly lowered prices for its branded product, and—even with the entry of a generic EpiPen (Teva) and the re-entry of kaléo’s Auvi-Q epinephrine autoinjector—has nonetheless retained its dominant position in the marketplace.³¹ Another epinephrine autoinjector, Impax’s Adrenacllick, is different enough—in design at least—to make it a less desirable alternative for many patients.³² Jonathan D. Alpern and William M. Stauffer have complained that “[w]ithout [yet] other competitors, history tells us not to expect significant cost savings anytime soon for this much-needed medicine.”³³

Much of the commentary on the persistently high price of EpiPen, specifically, has considered Mylan’s conduct through the lens of antitrust law.³⁴ Michael A. Carrier and Carl J. Minniti III, for example, examined three facets of Mylan’s conduct—Mylan’s predecessor’s settlement with Teva, its citizen petitions to the FDA about competing products, and its exclusive supply agreements with schools and Medicaid programs—as possible antitrust violations.³⁵ This “full range of

²⁹ See Ed Silverman, *Mylan Board Survives Ouster Attempt, but Shareholders Reject Rich Pay Packages*, STAT NEWS (June 22, 2017), <https://www.statnews.com/pharmalot/2017/06/22/mylan-board-vote> [<https://perma.cc/DMX9-NMGA>] (discussing shareholders’ displeasure with the negative perception surrounding the company).

³⁰ The term “authorized generic” refers to a drug that is the same as the approved brand name drug, but “that is marketed without the brand name on its label.” *FDA List of Authorized Generic Drugs*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/fda-list-authorized-generic-drugs> [<https://perma.cc/7H3X-VA4K>] (last updated Apr. 1, 2021).

³¹ See Letter from Vincent Sansone, Deputy Dir., Off. of Regul. Operations, U.S. Food & Drug Admin., to Cory Wohlbach, Senior Dir., U.S. Generics Regul. Affs., Teva Pharms. USA, Inc. (Aug. 16, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/090589Orig1s000ltr.pdf [<https://perma.cc/2XFM-BJNU>] (approving the ANDA for Teva’s generic EpiPen); Matthew Herper, *EpiPen Competitor Auvi-Q to Return to Market, Promising Lower Costs for Patients*, FORBES (Oct. 26, 2016), <https://www.forbes.com/sites/matthewherper/2016/10/26/epipen-competitor-auvi-q-to-return-to-market-promising-lower-costs-for-patients/?sh=14d0502576df> [<https://perma.cc/72NK-D5EF>] (describing kaléo’s plans for beginning to market Auvi-Q again in 2017).

³² See W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 807 (2020) (“The Adrenacllick, the closest competitor [to the EpiPen], is just a little bit different than the EpiPen The differences are minor, and certainly not improvements; it is hard to see a reason for them besides avoiding the EpiPen patents, especially since the Adrenacllick was developed well after the EpiPen.”).

³³ Jonathan D. Alpern & William M. Stauffer, *Does a Generic EpiPen Mean Lower Prices? Don’t Hold Your Breath*, STAT NEWS (Sept. 7, 2018), <https://www.statnews.com/2018/09/07/generic-epipen-teva-lower-prices> [<https://perma.cc/PT5C-34WN>].

³⁴ See, e.g., sources cited *supra* note 6.

³⁵ Carrier & Minniti, *supra* note 6, at 53.

behavior,” concluded Carrier and Minniti, “raises significant antitrust concerns and deserves a thorough investigation.”³⁶ Others have considered a wide range of causes of, and issues associated with, high prescription drug prices in general, including the industry’s moral obligations and the role of state law.³⁷

But Mylan’s power to make its own market can also be understood as arising from a synergistic intersection of patents, FDA law and policy, and the emergency context in which EpiPens are used. Under the Federal Food, Drug, and Cosmetic Act, EpiPen is a “combination product,” i.e., “[a] product comprised of two or more regulated components, [e.g.,] drug/device.”³⁸ This status has enabled Mylan to add patents covering the *device* component of EpiPen (and its improvements) to the “Orange Book”—a list of FDA-approved *drugs* and their attendant patents and regulatory exclusivities. This is important because the Orange Book plays a significant role in determining when generic competition can enter the market.³⁹ The ability to list *device* patents in the Orange Book, thus, gives Mylan an advantage compared to manufacturers of simple drug products because the FDA otherwise prohibits adding to the Orange Book a variety of patents untethered to the drug’s

³⁶ *Id.* at 72.

³⁷ See, e.g., David A. Hyman & Charles Silver, *Why Are We Being Overcharged for Pharmaceuticals? What Should We Do About It?*, 39 J. LEGAL MED. 137, 137–38 (2019) (discussing the role of price indices for high drug prices); Aaron S. Kesselheim, Michael S. Sinha, Jerry Avorn & Ameet Sarpatwari, *Pharmaceutical Policy in the United States in 2019: An Overview of the Landscape and Avenues for Improvement*, 30 STAN. L. & POL’Y REV. 421, 453 (2019) (discussing numerous issues relating to high drug prices); see also Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991, 1993 (2018) (describing drug pricing as one health technology policy problem for which the relationships between agencies are important); see generally Isaac D. Buck, *The Drug (Pricing) Wars: States, Preemption, and Unsustainable Prices*, 99 N.C. L. REV. 167 (2020) (discussing the intersection of high drug prices and vertical federalism); Michelle M. Mello & Rebecca E. Wolitz, *Legal Strategies for Reining in “Unconscionable” Prices for Prescription Drugs*, 114 NW. U. L. REV. 859 (2020) (discussing numerous issues relating to high drug prices); Govind Persad, *Pricing Drugs Fairly*, 62 WM. & MARY L. REV. 929 (2021) (same); Persad, *supra* note 3 (examining companies’ moral duties to patients in need of their products); Wolitz, *supra* note 3 (discussing the absence of legal duties related to companies’ commanding high drug prices).

³⁸ 21 C.F.R. § 3.2(e)(1) (2020); see also 21 U.S.C. § 353(g) (describing combination products and explaining the FDA’s regulatory scheme for such products).

³⁹ See generally U.S. FOOD & DRUG ADMIN., ORANGE BOOK QUESTIONS AND ANSWERS GUIDANCE FOR INDUSTRY: DRAFT GUIDANCE (May 2020), <https://www.fda.gov/media/138389/download> [<https://perma.cc/9BHA-LJFW>]. For example, if a company would like to market its generic product before all patents listed in the Orange Book for the branded product have expired, it files what is known as a “Paragraph IV certification.” *Id.* at 10–11. As Dmitry Karshedt has explained, “[t]he filing of a Paragraph IV certification is deemed by statute to be an act of patent infringement that allows the parties to initiate a lawsuit . . . which in turn triggers an automatic 30-month stay against [the FDA’s] approval of the [generic drug].” Dmitry Karshedt, *The More Things Change: Improvement Patents, Drug Modifications, and the FDA*, 104 IOWA L. REV. 1129, 1149 (2019). For further discussion of the Orange Book’s role as a “critical link between patent and FDA-regulatory aspects of pharmaceuticals” that helps determine when generic competition reaches the market, see *id.* at 1148–49.

pharmaceutical composition.⁴⁰ That is, this allows Mylan to use patents that would not otherwise be available to block generic competition for EpiPen. Furthermore, in the context of a product intended for emergencies for which people often incur significant out-of-pocket costs, this wrinkle has been one key to Mylan's power over the epinephrine autoinjectable market.

II

EPIPEN'S PATENTS AND GENERIC COMPETITION

One reason Mylan retains a dominant market position for epinephrine autoinjectors is that, unlike some drugs involved in recent pricing controversies,⁴¹ Mylan's EpiPen is not a generic product; it is a branded drug still protected by its own patents. This may be surprising given that basic syringes are centuries old and epinephrine has been used for over 100 years.⁴² But the key differences between EpiPen and what came before it are the specifics of the product's design: the quantity and stability of epinephrine in the syringe, the length of the needle, the physical stability of the device's safety release, the ease and time for self-injection, and the dispersion and uptake of epinephrine in the body.⁴³ These design elements allow EpiPens to be safely used by anyone, even those without specialized medical training, in tense, life-threatening emergencies.⁴⁴

The functional design elements of the autoinjector, rather than the drug itself, give patent protection to EpiPen. While EpiPen's original design stems from a 1977 patent from one of Mylan's predecessors, Meridian Medical Technologies, the design has been reworked over the years in response to safety concerns, like accidental autoinjection.⁴⁵ On these improvements, Meridian received at least five patents, all expiring on September 11, 2025.⁴⁶ One was listed in the Orange Book

⁴⁰ See 21 C.F.R. § 314.53(b) (2020).

⁴¹ See, e.g., Chintan V. Dave, Aaron S. Kesselheim, Erin R. Fox, Peihua Qiu & Abraham Hartzema, *High Generic Drug Prices and Market Competition: A Retrospective Cohort Study*, 167 ANNALS INTERNAL MED. 145, 145 (2017) (noting recent pricing controversies involving companies like Turing and Valeant).

⁴² See *supra* notes 14–15 and accompanying text.

⁴³ See Robert L. Hill, John G. Wilmot, Beth A. Belluscio, Kevin Cleary, David Lindisch, Robin Tucker, Emmanuel Wilson & Rajesh B. Shukla, *Comparison of Drug Delivery with Autoinjector Versus Manual Prefilled Syringe and Between Three Different Autoinjector Devices Administered in Pig Thigh*, 9 MED. DEVICES: EVIDENCE & RSCH. 257, 257 (2016); Andreas Schwirtz & Harald Seeger, *Comparison of the Robustness and Functionality of Three Adrenaline Auto-Injectors*, 5 J. ASTHMA & ALLERGY 39, 45 (2012) (noting advantages of cartridge-based designs—including EpiPen's—over syringe-based designs).

⁴⁴ Schwirtz & Seeger, *supra* note 43, at 43.

⁴⁵ See Narayan Deshmukh & J. Timothy Tolland, *Treatment of Accidental Epinephrine Injection in a Finger*, 7 J. EMERGENCY MED. 408, 408 (1989) (documenting a school nurse's accidental injection).

⁴⁶ *Patent and Exclusivity for: N019430*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=019430&Appl_type=N [<https://perma.cc/D9UU-NCP6>] (last visited June 10, 2021).

by Mylan as recently as 2017, at perhaps the height of EpiPen's pricing controversy.⁴⁷

Alongside Mylan's government outreach, consumer awareness of the product, and EpiPens' safety profile, these patents have significantly suppressed competition. Generally, drug manufacturers who wish to create a generic version of a patented drug must first challenge the drug's Orange Book-listed patents in court.⁴⁸ This is a time-consuming, laborious, and, above all, costly process. A 2019 report by the American Intellectual Property Law Association pegged a typical pharmaceutical lawsuit as costing each side approximately \$7 million in attorneys' fees alone.⁴⁹ Nonetheless, several companies did indeed challenge Mylan's new EpiPen patents, notably Teva Pharmaceuticals in 2009.⁵⁰ After three years of litigation, Mylan and Teva settled their patent dispute in 2012, with the agreement that Teva would be able to sell a true generic EpiPen by mid-2015.⁵¹ But difficulties with the FDA's approval process—according to Mylan, Teva's autoinjector was slightly different and less safe—prevented Teva from coming to market until 2018.⁵² Other companies, like Sanofi, have attempted to circumvent Mylan's patents by using different forms of the autoinjector.⁵³ But safety concerns for those products, too, have slowed their widespread adoption.⁵⁴ In Sanofi's case, its epinephrine autoinjector product, Auvi-Q, was voluntarily recalled by the company in 2015⁵⁵ and not reintroduced until 2017 (after Sanofi returned marketing rights to kaléo).⁵⁶

In some ways, this is unsurprising. Part of the Hatch-Waxman Act's "delicate" compromise between innovation and competition centers on patents as the principal instruments keeping generics at bay.⁵⁷ Broadly speaking, the FDA cannot approve a

⁴⁷ See *id.* (listing U.S. Patent No. 9,586,010 on May 12, 2017).

⁴⁸ See Jacob S. Sherkow, *Administrating Patent Litigation*, 90 WASH. L. REV. 205, 214–15 (2015) (noting that FDA approval of generic versions of patented drugs requires a final resolution of the patent dispute).

⁴⁹ AM. INTELL. PROP. L. ASS'N, 2019 REPORT OF THE ECONOMIC SURVEY 50–71 (2019), <https://www.aipla.org/detail/journal-issue/2019-report-of-the-economic-survey>.

⁵⁰ Carrier & Minetti, *supra* note 6, at 59–64.

⁵¹ *Id.* at 60.

⁵² See *id.* at 64–66; Michael Erman & Jillian Mincer, *Exclusive: Teva's Generic EpiPen Launch Stalls Months After Approval*, REUTERS (Jan. 31, 2019), <https://www.reuters.com/article/us-teva-pharm-ind-epipen-exclusive/exclusive-tevas-generic-epipen-launch-stalls-months-after-approval-idUSKCN1PP2BU> [<https://perma.cc/QL4N-3AWW>].

⁵³ See Meghana Keshavan, *5 Reasons Why No One Has Built a Better EpiPen*, STAT NEWS (Sept. 9, 2016), <https://www.statnews.com/2016/09/09/epipen-lack-of-innovation/> [<https://perma.cc/U7W4-CXTL>] (describing Auvi-Q).

⁵⁴ *Id.*

⁵⁵ Auvi-Q *Epinephrine Auto-Injector Returns*, 59 MED. LETTER ON DRUGS & THERAPEUTICS 33, 33 (2017).

⁵⁶ *Id.*

⁵⁷ See Erika Lietzan, *The History and Political Economy of the Hatch-Waxman Amendments*, 49 SETON HALL L. REV. 53, 100, 102, 105 (2018) (describing but rejecting the common perception that the Hatch-Waxman Act was struck as a compromise during the legislative process).

generic version of a drug until the patents listed in the Orange Book covering the branded drug expire or are shown to be invalid or not infringed.⁵⁸ Such patents—at least, as traditionally contemplated—typically cover the active ingredient and its pharmaceutical composition, e.g., the drug and its tablet (or other dosage form), in addition to its methods of use.⁵⁹ Indeed, to limit the patents that drug developers can assert against generics, the FDA refuses to include in the Orange Book a variety of patents covering aspects of the product other than the medicament itself.⁶⁰ Once the principal patents covering the product and its use expire, variations on other components of the product, such as the processes for making it or the drug’s packaging, should not be arbiters of generic competition.⁶¹

Yet EpiPen’s patent protection on the *autoinjector*—rather than the solution inside of it—is atypical,⁶² and gives rise to particular inefficiencies under the Hatch-Waxman Act. Given the importance of the autoinjector itself to emergency epinephrine products—as demonstrated by Teva and Sanofi’s difficulties in manufacturing a suitable autoinjector—patents covering EpiPen’s device and its safety enhancements have the power to stymie generic competition, long after either the drug or the device were first used.⁶³ Small changes, like the cover of the needle, can thwart generic entry.⁶⁴ While this may seem like an opportunity to design around these changes to avoid infringement, modifications to the autoinjector may make the product less safe—as was the case with Sanofi’s difficulties producing Auvi-Q.⁶⁵ In addition, and for EpiPen specifically, consumers’ familiarity with EpiPen’s precise functionality may discourage them from trying noninfringing variants of the product—such as Adrenacllick—even if those have been demonstrated to be safe.⁶⁶

⁵⁸ 21 U.S.C. § 355(c)(3); *see also* Karshedt, *supra* note 39, at 1149–50 (describing the process for and stakes of challenging patents listed in the Orange Book).

⁵⁹ *See* Sherkow, *supra* note 48, at 233–34 (describing the phenomenon of “product hopping,” where manufacturers make minimal changes to patented drugs to prevent competition from generic products).

⁶⁰ 21 C.F.R. § 314.53(b) (2020) (“Process patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.”).

⁶¹ *See* Sherkow, *supra* note 48, at 252–53 (describing the role that refusing to list patents under 21 C.F.R. § 314.53 plays in approving generic applications).

⁶² *Cf.* Listing of Patent Information in the Orange Book, 85 Fed. Reg. 33,169, 33,172 (June 1, 2020) (acknowledging “uncertainty” about whether certain “device-related patents” may be submitted to the Orange Book).

⁶³ *See* Carrier & Minniti, *supra* note 6, at 59–64 (arguing that Mylan has used these patents to block generic competition).

⁶⁴ *See* Automatic Injector with Needle Cover, U.S. Patent No. 9,586,010, at [57] (filed Mar. 7, 2013) (issued Mar. 7, 2017) (describing an autoinjector with a novel “needle cover operative to engage an injection site and activate the injector”).

⁶⁵ *See* Auvi-Q *Epinephrine Auto-Injector Returns*, *supra* note 55, at 33 (noting previous safety concerns).

⁶⁶ *See* Price, *supra* note 32, at 808 (“Although the differences between the EpiPen, Adrenacllick, and Auvi-Q are not especially large, they matter a great deal to patients—especially children—who use them in high-stress emergency situations.”).

With self-administered emergency medicines, which require trust and familiarity for their safe and effective use, and where seconds can be the difference between life and death, no one wants to stop to consult a manual.⁶⁷ In this sense, patents covering the autoinjection device protect an aspect of real-world drug safety for which people may not have an unfettered choice. However, what allows such patents to be listed in the Orange Book in the first instance is a function of FDA law and policy.

III

DRUG-DEVICE COMBINATION PRODUCTS AND THE FDA'S ROLE

Although the FDA does not have the authority to directly regulate drug prices, the FDA's regulatory scheme can play a role in drug pricing, as demonstrated in the EpiPen pricing controversy. Perhaps the most well-known aspect of the FDA's regulatory regime is its gatekeeping role for medical products—new drugs, and many devices, cannot be marketed in the United States before the manufacturer demonstrates to the FDA that the products are safe and effective for their intended use.⁶⁸ This requirement may slow the entry of competing products to the market even when patents and regulatory exclusivity do not limit competition, as shown by the experiences of Teva and Sanofi with their epinephrine autoinjectors, but rightfully so. Patients and the public health are not served by access to ineffective or unsafe medical products, and it takes time to do the research necessary to develop sufficient information about product safety and effectiveness.⁶⁹

EpiPen and other autoinjectors, as explained above, are neither solely drugs nor solely devices. Instead, under the Federal Food, Drug, and Cosmetic Act, they are “combination products” because they comprise both a drug (epinephrine) and a device (the autoinjector).⁷⁰ When faced with a combination product, the FDA must determine the “primary mode of action”⁷¹—that which “provides the most important

⁶⁷ *See id.*

⁶⁸ *See, e.g.*, 21 U.S.C. § 355(a), (d) (setting forth the new drug approval requirement and the standard for such approval).

⁶⁹ *See* U.S. FOOD & DRUG ADMIN., MEMORANDUM: PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 4–5 (2017), https://downloads.regulations.gov/FDA-2016-N-1149-0040/attachment_1.pdf [<https://perma.cc/7S8E-JCYP>]; *see also* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMMS. & TECH. L. REV. 345, 348 (2007) (“Although premarket approval is understood primarily as a consumer protection measure, in the past twenty years Congress has repeatedly fine-tuned the FDA’s mandate as a market gatekeeper in ways that might be better understood in terms of innovation policy . . .”).

Ineffective medicines may further put significant strain on the public fisc. *See, e.g.*, Nicholas Bagley & Rachel Sachs, *The Drug That Could Break American Health Care*, ATLANTIC (June 11, 2021), <https://www.theatlantic.com/ideas/archive/2021/06/aduhelm-drug-alzheimers-cost-medicare/619169> [<https://perma.cc/R879-K69H>] (describing how the approval of aducanumab for Alzheimer’s disease “could trigger hundreds of billions of dollars of new government spending”).

⁷⁰ 21 U.S.C. § 353(g).

⁷¹ *Id.*

therapeutic action”⁷²—and regulate the product according to that mode of action. Generally, prefilled syringes and delivery systems are regulated as drugs because the device’s purpose is only to deliver the drug, which is the component that produces the desired effect or treats the disease or condition.⁷³ EpiPen’s classification as a combination product that is regulated as a drug, therefore, is not a result of any particular action or strategy by Mylan but instead a result of federal law, FDA regulations, and longstanding FDA policy.

But it is this regulatory structure that has empowered Mylan’s patent strategy. The classification of EpiPen, even partially, as a *drug* brings Mylan’s *device* into the Hatch-Waxman Act regime, allowing Mylan to list any patents not otherwise prohibited by the FDA in the Orange Book.⁷⁴ Typically, the FDA does not refuse to authorize medical devices because of latent patent issues between competitors,⁷⁵ while classification as a drug requires the FDA to delay approval of generics until patent infringement issues have been resolved.⁷⁶ When it comes to the EpiPen, by contrast, patents covering the *device* have hampered the FDA from approving generic products.⁷⁷

To be sure, this regulatory structure has its merits. The FDA has acknowledged that combination products can be more challenging to develop than traditional products.⁷⁸ Accordingly, robust incentives to develop such products, like patents, may be useful. Additionally, some have argued that the approval standard for drugs is stricter than for devices,⁷⁹ and so, by extension, approval for drug-device combination products, under new drug applications, should be stricter than for devices alone. And, in contrast to medical devices, which operate under an entirely

⁷² 21 C.F.R. § 3.2(m) (2020).

⁷³ Carl C. Peck & James S. Benson, *Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health*, FDA (Oct. 31, 1991), <https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121177.htm> [<https://perma.cc/BLE8-VXF4>] (describing the regulatory scheme for such “prefilled delivery system[s]”).

⁷⁴ See Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36,676, 36,680 (June 18, 2003) (“[I]f the patent claims the drug product . . . the patent must be submitted for listing.”).

⁷⁵ See, e.g., Patricia J. Zettler & Erika Lietzan, *Regulating Medical Devices in the United States*, in THE OXFORD HANDBOOK OF COMPARATIVE HEALTH LAW 758–63, 770–71 (David Orentlicher & Tamara K. Hervey eds., 2020) (describing the premarket authorization pathways for devices as well as the role of patents in device innovation).

⁷⁶ See 21 U.S.C. § 355(j)(2)(vii).

⁷⁷ See *supra* notes 41–47 and accompanying text.

⁷⁸ See, e.g., *Reviewing the Rising Price of EpiPens: Hearing Before the H. Comm. on Oversight & Gov’t Reform*, 114th Cong. 10 (2017) (statement of Douglas C. Throckmorton, Deputy Dir. for Regul. Programs, U.S. Food & Drug Admin.) (“FDA understands that development of combination products can be more challenging than for typical drug products.”).

⁷⁹ E.g., Peter Barton Hutt, Richard A. Merrill & Alan M. Kirschenbaum, *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605, 605–06 (1992).

different patent and approval regime,⁸⁰ situating drug-device combination products within the Hatch-Waxman Act at least gives potential competitors notice of which patents they may be sued on.⁸¹ The FDA's combination-product regulatory structure may therefore optimally align Mylan's and the public's interests regarding innovation, safety, and effectiveness. Unlike the vast majority of garden-variety generic drugs, safety and manufacturing issues did, indeed, affect EpiPen's generic competitors;⁸² making ready-to-use, shelf-stable autoinjectors is hard.⁸³

And yet, EpiPen's immediate life-or-death importance and the access problems that people have faced due to pricing evoke salient questions about whether the current regulatory structure is, in fact, the optimal one. To start, the FDA may want to revisit listing device patents on drug-device combination products approved under new drug applications in the Orange Book. The FDA has long claimed its authority to police the Orange Book is "purely ministerial."⁸⁴ And while that may be how the Agency sees its role,⁸⁵ it is also the case that the FDA already bans listing various patents unrelated to the drug product in the Orange Book.⁸⁶ It seemingly could do the same for device patents on drug-device combination products. Indeed, the Agency has itself signaled possible interest in changing its current approach: In June 2020 it published a Notice in the Federal Register seeking public comment on the listing of patents covering device components of drug-device combination products, among other Orange Book issues.⁸⁷

⁸⁰ See generally Adam Lewin, *Medical Device Innovation in America: Tensions Between Food and Drug Law and Patent Law*, 26 HARV. J.L. & TECH. 403, 415–27 (2012) (describing patents' role in medical device approval).

⁸¹ Cf. Teva Pharms. USA, Inc., Comment on Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") and Listing of Patent Information in the Orange Book 6 (Aug. 31, 2020), https://downloads.regulations.gov/FDA-2020-N-1127-0010/attachment_1.pdf [<https://perma.cc/YK3S-KNFS>] (commenting, in response to FDA's Notice, "Teva generally believes that all patents which claim an integrated device component of an approved NDA product (or a method of using such an integrated device component) and which have the potential to block the marketing of an approved follow-on product should be listed in the Orange Book").

⁸² See *supra* notes 52–56 and accompanying text.

⁸³ Keshavan, *supra* note 53.

⁸⁴ See, e.g., *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237 (4th Cir. 2002) ("The FDA defends this purely ministerial conception of its role in the Orange Book listing process by explaining that it lacks both the resources and the expertise to police the correctness of Orange Book listings.").

⁸⁵ See, e.g., *id.* at 230 (affirming that the Federal Food, Drug, and Cosmetic Act "assigns the FDA a purely ministerial role regarding Orange Book listings").

⁸⁶ 21 C.F.R. § 314.53(b) (2020).

⁸⁷ 85 Fed. Reg. 33,169, 33,173 (June 1, 2020); see also Mylan, Comment on Listing of Patent Information in the Orange Book, at 4–6 (Aug. 31, 2020), https://downloads.regulations.gov/FDA-2020-N-1127-0018/attachment_1.pdf [<https://perma.cc/ER9Z-PM2P>] ("The FDA should accept device patents for listing in the Orange Book, but only if the device constituent part of a drug product claimed in the patent is integral to the drug's delivery system and is reviewed and approved as part of the NDA."); Teva Pharms. USA, Inc., *supra* note 81, at 6 ("Teva generally believes that all patents . . . which have the potential to block the marketing of an approved follow-on product should be listed in the Orange Book.").

If patents covering device components were no longer listed, whatever device-related patent infringement issues exist between a brand combination product and possible generics could simply be litigated *post*-approval, against the backdrop of whatever price pressures such litigation yields.⁸⁸ This would give the public access to the generic product while the surrounding patent litigation takes its course. To be fair, such litigation may yield arguably anticompetitive settlements, as described by Carrier and Minniti,⁸⁹ no different from those that arose concerning EpiPen. But even then, such settlements would not be predicated on FDA approval, as they are now. This removes a rather heavy cudgel from brand manufacturers' armory for keeping competition—and importantly, price competition—at bay. Although changing how and whether device patents are listed in the Orange Book is not a comprehensive solution to the kinds of pricing concerns highlighted by the EpiPen controversy, it is one action that one agency could take under existing law that might help. As Michelle M. Mello and Trish Riley explained, “the battle against drug overpricing is more likely to be fought with a thousand arrows than [one] silver bullet.”⁹⁰

Beyond these kinds of tweaks, however, it may be worth considering more radical changes to the FDA's approach in specific contexts like that of EpiPen, i.e., emergency medicines intended for lay administration. To be clear, drug pricing for such medicines is an immediate—and urgent—public health concern that presents complicated issues ideally addressed through numerous reforms, many of which are, frankly, beyond the scope of the FDA's current authority and expertise.⁹¹ But, in the absence of such reforms and assuming political appetite for changing the FDA's authority to tackle these issues more directly, one possibility may be for the FDA, in certain circumstances, to clearly acknowledge the relationship between price, patient access, and health risks, and to consider that relationship in making its regulatory decisions.⁹² But again, this would likely be only a single bullet—and not

⁸⁸ This occurs in other biopharmaceutical contexts; for example, patent suits between marketers of two independently approved (i.e., non-generic) drugs or biologics. Amgen's biologic, Repatha, and Sanofi's biologic, Praluent, both target the same molecule, PCSK9, and were separately approved for virtually identical indications; a post-approval patent suit between the two companies led to the lowering of prices for each. Ned Pagliarulo, *Amgen Patents on Repatha Invalid, Judge Rules in Reversal*, BIOPHARMA DIVE (Aug. 28, 2019), <https://www.biopharmadive.com/news/amgen-patents-on-repatha-invalid-judge-rules-in-reversal/561882> [<https://perma.cc/ZY3M-6TLW>].

⁸⁹ See Carrier & Minniti, *supra* note 6, at 62–63.

⁹⁰ Michelle M. Mello & Trish Riley, *To Address Drug Affordability, Grab the Low-Hanging Fruit*, JAMA HEALTH F., at 2 (Feb. 25, 2021), <https://jamanetwork.com/channels/healthforum/fullarticle/2777036> [<https://perma.cc/SYP9-UT7V>].

⁹¹ See, e.g., *id.*; Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 862 (2016).

⁹² Cf. Craig J. Konnoth, *Drugs' Other Side-Effects*, 105 IOWA L. REV. 171, 236 (2019) (arguing

a silver one—in a larger battle concerning drug pricing and emergency medicines.⁹³

Were the FDA to engage in such an analysis, it could begin by acknowledging that lower-quality emergency autoinjectors are more likely to cause grave harm. But this potential for harm perhaps should be balanced against the contextual risk under which these products are used. Emergency medicines are, by definition, those used in life-or-death situations—and yes, quality differences among emergency medicines may mean the difference between life or death. A person's means should not dictate the care they receive.⁹⁴ But this is complicated where—as with EpiPen—price is, in fact, a major determinant of access, and it may be that small differences in the benefit-risk profiles of epinephrine autoinjectors would be acceptable to people given this reality. In those circumstances, for at least some patients, the comparison may not be between an optimal, but expensive, product and a cheaper one associated with more uncertainty—it may be between EpiPen or nothing at all. Indeed, following EpiPen's pricing controversy, people described hoarding EpiPens, keeping them after they had expired due to the product's high price, and forgoing purchases altogether.⁹⁵

As currently structured, price is not explicitly a factor in the FDA's benefit-risk analysis for approval.⁹⁶ Congress seemingly structured the FDA's approval authority with the presumption that patients will have access to the drug once approved, describing safety and effectiveness without express reference to price.⁹⁷

that FDA should take a broader perspective on what counts as relevant information about risks and benefits of drugs, noting that “[w]hile the FDA might run into political roadblocks if it refused to approve an application solely because of projected price, having the information would allow it to begin discussions with stakeholders about how to limit the public health effects of drug prices if the drug were approved”); Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 *FOOD & DRUG L.J.* 221, 223–24 (2018) (arguing that FDA should incorporate broader public health information into approval decisions for certain drug classes). Such a relationship is all the more important where a largely ineffective medicine financially threatens public payers. See Bagley & Sachs, *supra* note 69.

⁹³ See Mello & Riley, *supra* note 90, at 2 (“[I]n the US, the battle against drug overpricing is more likely to be fought with a thousand arrows than 1 silver bullet.”).

⁹⁴ Cf. Persad, *supra* note 37, at 936–37, 942 (explaining “conceptions of fairness in drug pricing”).

⁹⁵ Ike Swetlitz, *High Price of EpiPens Spurs Consumers, EMTs to Resort to Syringes for Allergic Reactions*, STAT NEWS (July 6, 2016), <https://www.statnews.com/2016/07/06/epipen-prices-allergies> [<https://perma.cc/7AJJ-QQFT>]. Still others have advocated that patients make their own epinephrine autoinjectors. See Patricia J. Zettler, Christi J. Guerrini & Jacob S. Sherkow, *Finding a Regulatory Balance for Genetic Biohacking*, in CONSUMER GENETIC TECHNOLOGIES: ETHICAL AND LEGAL CONSIDERATIONS (I. Glenn Cohen, Nita Farahany, Henry T. Greely & Carmel Shachar eds., forthcoming 2021) (manuscript at 4) (on file with the *New York University Law Review*), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3490006.

⁹⁶ See, e.g., Konnoth, *supra* note 92, at 236 (considering whether price should be a factor in the approval process); see also 21 U.S.C. § 355(d), (j) (providing the statutory criteria for approval of new drug applications and abbreviated new drug applications).

⁹⁷ See 21 U.S.C. § 355(d), (j).

But with respect to emergency medicines with significant costs, such as EpiPen, price may be an element of whether or not patients use the drug at all. This is arguably analogous to a drug's pharmaceutical tolerability or its method of administration, which the Agency does consider.⁹⁸

Moreover, there is at least one instance in which the Agency has appeared to consider the relationship between price and patient access, though not in the context of an approval decision. After the 2011 approval of the drug Makena for preterm labor—a branded version of a drug that had been sold at low cost for over fifty years through compounding pharmacies—the manufacturer set the price at \$1,500 per dose.⁹⁹ As with EpiPen, this price sparked outrage and Congressional hearings.¹⁰⁰ The FDA ultimately took the unusual step of announcing that it would not take enforcement action against compounding pharmacies that continued to make and sell the drug—thereby allowing patients to access cheaper,¹⁰¹ albeit illegal, unapproved versions of the drug manufactured with fewer safeguards.¹⁰²

To be clear, this is not to say the statutory standards of safety and effectiveness should not apply to epinephrine autoinjectors. FDA oversight and approval are crucially important for public health. Flooding the market with poor emergency medicines is liable to harm people who otherwise rely on the Agency's oversight, cause the public to lose trust in the FDA and pharmaceuticals more broadly, and diminish the essential information-production value that FDA gatekeeping serves.¹⁰³ Allowing unfettered competition from less-regulated products also may have unintended consequences, such as undermining companies' ability to meet higher standards and continue to be financially viable—for example, Makena's manufacturer filed for bankruptcy in the wake of the FDA's decision not to enforce against entities compounding versions of the drug.¹⁰⁴ Moreover, measuring any

⁹⁸ See, e.g., U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: PATIENT-FOCUSED DRUG DEVELOPMENT: METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS 35, 45 (2019), <https://www.fda.gov/media/131230/download> [<https://perma.cc/2XCG-GHPX>] (describing helpful methods to obtain patient feedback on “tolerability” and “[t]reatment burden,” the latter of which includes method of administration).

⁹⁹ Erika Lietzan, *Access Before Evidence and the Price of the FDA's New Drug Authorities*, 53 U. RICH. L. REV. 1243, 1277 (2019). More specifically, Makena is a branded version of hydroxyprogesterone caproate, which had been marketed since before Congress created the modern drug approval process in 1962. At the time of Makena's approval, hydroxyprogesterone caproate was widely available at a cost of \$10 to \$20 per dose through compounding pharmacies. *Id.* at 1276–77.

¹⁰⁰ *Id.* at 1277–78.

¹⁰¹ *Id.* at 1278; Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396, 404–05 (2015).

¹⁰² Cf. Kevin Outterson, *Regulating Compounding Pharmacies After NECC*, 367 NEW ENG. J. MED. 1969, 1969, 1971 (2012) (describing a contemporaneous fungal meningitis outbreak associated with compounded drugs that killed dozens of people).

¹⁰³ See, e.g., Eisenberg, *supra* note 69, at 347–48 (describing the information-generating value of the FDA approval process).

¹⁰⁴ Lietzan, *supra* note 99, at 1278.

tradeoff in price and access versus changes to the product's benefit-risk profile is likely to be practically difficult—and we do not attempt to do so here. And transparently including such a tradeoff in its assessment of a drug-device combination product, for the purpose of approval, would be a radical departure from the FDA's general practice, likely posing legal and political risks for the Agency. But, within the context of drug-device combination products like EpiPen for which price can have immediate life-or-death consequences, it is worth lawmakers and the Agency at least considering some bold measures.

CONCLUSION

Much of the outrage over EpiPen's persistently high prices focuses on the product's role as an emergency medicine in connection with Mylan's putatively anticompetitive conduct.¹⁰⁵ These criticisms are important. But an additional wrinkle is the connection between patents and the FDA's role in governing drug-device combination products. Currently, makers of drug-device combination products, like EpiPen, list certain patents covering the drug and device components of their product in the Orange Book. This makes sense with respect to the drug component of a product. But listing the device patents as well alters the usual tradeoff between possible infringement and approval for drugs and devices, centering Hatch-Waxman Act patent litigation on the *device* and its improvements. This contributes to high prices for brand combination products, a particularly pernicious problem in the context of emergency medicines for which patients may face high out-of-pocket costs.

This is not to say that the device components of combination products are not a critically important focus of safety and effectiveness. They are, and EpiPen provides, in many ways, a cautionary tale about presuming that complex manufacturing for autoinjectors can be easily accomplished for generics. That said, refusing to list device patents in the Orange Book is low-hanging fruit¹⁰⁶ for drug-patent reform; the FDA does not otherwise tie the approval of devices to device patents. Making such changes in Orange Book practice—especially for autoinjectable emergency medicines—would foster generic entry, put downward pressure on prices for such products, and broaden patient access. For many drugs, the connection between patents and prices is often opaque. But for combination-product emergency medicines like EpiPen, the connection between patents and prices may be the difference between life and death.

¹⁰⁵ See sources cited *supra* note 6.

¹⁰⁶ Cf. Mello & Riley, *supra* note 90, at 1 (identifying other “[l]ow-[h]anging [f]ruit” for reining in drug prices).