Costly Gadgets: Barriers to Market Entry and Price Competition for Generic Drug-Device Combinations in the United States

Michael S. Sinha

Follow this and additional works at: https://scholarship.law.umn.edu/mjlst

Part of the Food and Drug Law Commons, and the Health Law and Policy Commons

Recommended Citation
Costly Gadgets: Barriers to Market Entry and Price Competition for Generic Drug-Device Combinations in the United States

Michael S. Sinha*

ABSTRACT

Prescription drug prices continue to rise unabated in the United States, largely due to a system that allows brand-name drug makers to charge whatever the market will bear. Some of the costliest pharmaceuticals in the United States—both by price and by total expenditure—are drugs that require a drug delivery device for proper use. Examples include respiratory inhalers, immunologic drugs, opioid overdose reversal drugs, patches for chronic pain, emergent anaphylaxis treatments, and insulin products. One of the ways manufacturers have successfully extended market exclusivity on such combination products is by pursuing tertiary patents on the device component of the product.

Once all patents have expired on a drug-device combination, generic entry has been further complicated by the FDA’s strict standards for approving “complex generic” products via the Abbreviated New Drug Application (ANDA) pathway. These additional requirements have proven particularly onerous for some generic firms, and given such obstacles to complex generic approval via the ANDA pathway, many companies have turned to an arguably more straightforward path to compete with drug-
device combinations that have expired patents: the 505(b)(2) new
drug approval (NDA) pathway.

This manuscript takes the following format: (1) a detailed
explanation of the various challenges to generic competition in
combination products; (2) a description of the FDA’s complex
generic ANDA approval process and experience to date; (3) three
empirical case studies that provide real-world perspective to
these market inefficiencies; and (4) proposed solutions for
Congress, the FDA, and other key stakeholders as they attempt
to address the high cost of pharmaceutical-device combinations
in the United States.

I. Introduction ................................................................. 295

II. Drug Pricing in the United States .................. 300
   A. Drugs Are Priced at Whatever the Market Will
      Bear ................................................................. 300
   B. Patients Struggle To Afford Medications..... 302

III. Combination Products ............................... 303
   A. Listing of Patents in the FDA’s Orange Book 305
   B. Product Lifecycle Management ............... 307
   C. Postmarket Research and Development ...... 307
   D. Evergreening: Secondary & Tertiary Patents 308
   E. Cost of Drug-Device Combination Products .. 311
   F. Competition and Drug-Device Combinations 312

IV. Generics for Combination Products ............... 313
   A. Interchangeability and Automatic
      Substitution .................................................. 315

V. The 505(b)(2) Pathway ........................................... 316
   A. Effect on Competition and Price .............. 316

VI. The FDA and Complex Generics: 3 Case Studies.... 318
   A. Case Study 1: Fluticasone/Salmeterol [Advair
      Diskus] ......................................................... 319
   B. Case Study 2: Adalimumab [Humira] ......... 331
   C. Case Study 3: Naloxone [Narcan and Evzio]. 345

VII. Policy Recommendations ........................................ 353
   A. Strengthen Initial FDA Review ................. 353
   B. Patent Reforms To Facilitate Market Entry of
      Competitors ................................................... 354
   C. Complex Generic ANDA or 505(b)(2)? Why Not
      a New Approach? ........................................... 355
   D. Curbing Incentives for Tertiary Patenting ... 358
   E. Fixing Biosimilars & Biologic Drug-Devices . 359

VIII. Conclusion ............................................................. 360
I. INTRODUCTION

Rising prices in the pharmaceutical sector have captured the attention of patients and policymakers alike over the last several years, particularly as lifesaving medications like epinephrine (EpiPen) and insulin (Lantus, Novolog) increase in price and costs shift to consumers. So, too, have the prices of expensive biologics like adalimumab (Humira) and etanercept (Enbrel), as well as respiratory inhalers like budesonide/formoterol (Symbicort) and fluticasone/salmeterol (Advair).

What do these products have in common? They are all designed for self-administration by patients, and all have associated devices (these will be defined for the purpose of this article as “drug-device combinations” or “combination products”). Combination products arguably improve patient usability and safety—an autoinjector “pen” is more user-friendly than a vial and a syringe. Combination products also tend to be less error-prone, allowing certain types of medications at specified doses to be administered conveniently at home; this improves adherence and reduces system costs as compared to physician office-based or infusion center-based administration of injectable medications. Other combination products seek to improve medication compliance, like the Abilify MyCite® digital pill, which generates an electrical signal when exposed to stomach fluid (an indication that the patient has swallowed the pill). Yet there may be a more insidious purpose for designing

1. I will be using these terms to characterize all products with an associated medical device, whether they be small-molecule drug, biologic, or biosimilar; see 21 C.F.R. § 3.2(e) (defining a “combination product” as “a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity” or separately packaged products intended to be used together). The term “drug-device combination” does not adequately characterize the variety of medicinal products that can be used in combination with a device. See also Philip E. Alford, Rethinking FDA Regulation of Complex Products, 21 MINN. J.L. SCI. & TECH. 477 (2020) (discussing other complex products, including drug-device combinations).

devices for combination products: to thwart generic entry and competition that would capture market share and cut into profit margins.

For brand-name pharmaceutical products, the manufacturer sets the list price at whatever the market will bear; nine out of every ten dollars spent on pharmaceutical products goes toward the purchase of brand-name drugs. The most reliable way to lower drug prices is via the introduction of generics, which end market monopolies and foster the development of a competitive market for a particular product. Yet there is often much uncertainty as to when generic entry will occur. Although regulatory and patent exclusivities can help pinpoint an expected date of generic entry, manufacturers often use a variety of anticompetitive strategies to delay generic entry and extend market monopolies.

(detailing how new systems like Abilify MyCite® can be used to facilitate adherence to treatment); Matthew Avery & Dan Liu, Bringing Smart Pills to Market: FDA Regulation of Ingestible Drug/Device Combination Products, 66 FOOD & DRUG L.J. 329, 330 (2011) (describing the development of smart pills and the ensuing regulatory processes).


8. See Gregory H. Jones, Michael A. Carrier, Richard T. Silver & Hagop Kantarjian, Strategies That Delay or Prevent the Timely Availability of Affordable Generic Drugs in the United States, 127 BLOOD 1398 (2016) (reviewing anticompetitive strategies that delay generic competition); see also
Less understood is the role of device components of medicinal products in (1) contributing to extended market exclusivity and high drug prices; and (2) impeding the entry of generic competitors. Generic competitors seeking to replicate such combination products have taken two distinct paths. The best-characterized pathway is the Abbreviated New Drug Application (ANDA).\(^9\) However, the process by which a manufacturer obtains ANDA approval for combination products is more complex than the process for small-molecule drugs. This process has been fraught with challenges—including rejected applications—in part because of stringent requirements of substantial similarity of device appearance and function.\(^10\)

In light of these challenges for combination products, generic competitors will often forgo the ANDA process in favor of a new drug application (NDA) through the 505(b)(2) approval pathway.\(^11\) Unlike the "standard" 505(b)(1) approval pathway, 505(b)(2) is designed for products for which components—usually small-molecule drugs—are already FDA-approved and have some data supporting their use.\(^12\) Though user fees for 505(b)(2) applications are higher than for ANDAs,\(^13\) applicants are able to rely on safety and efficacy data from the original manufacturer for 505(b)(2) approval, which reduces costs of pre-approval studies. Recognizing that generics of combination products with device components are more difficult to replicate and study than small-molecule generics, the FDA created a

---

10. See 21 C.F.R. § 314.110(a) (2020) (outlining how applicants receive a “complete response letter” from the FDA upon rejection of an application or abbreviated application).
12. See id.
Center for Research on Complex Generics\textsuperscript{14} in August 2020 to clarify the process for study and approval of such products.

Historically, most prescription drugs consisted of small molecules with simple chemical structures that are generally easy for generic manufacturers to replicate. Though brand-name drugs sell for high prices during the protected market exclusivity period, the expiration of exclusivity allows several generic competitors to quickly enter the market, leading to competition that has the effect of lowering drug prices dramatically over time.\textsuperscript{15} Use of generic small-molecule drugs has been credited with saving the United States health care system nearly $2.4 trillion in the last decade.\textsuperscript{16}

Biologic products have challenged this paradigm. Biologics—which include protein-based therapeutics, including cytokines, clotting factors, monoclonal antibodies, and enzymes—accounted for more than one-third of all new FDA approvals from 2015 to 2019.\textsuperscript{17} Biologics now comprise

\begin{itemize}
\item \textsuperscript{14} See CTR. FOR RSCH. ON COMPLEX GENERICS AT THE UNIV. OF MD., BALT. \& THE UNIV. OF MICH., http://www.complexgenerics.org/ (website for Center for Research on Complex Generics); see also U.S. FOOD \& DRUG ADMIN., GDUF A REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2018–2022 25 (2016), https://www.fda.gov/media/101052/download (noting that complex products include "complex drug-device combination products (e.g., auto injectors, metered dose inhalers").
\item \textsuperscript{16} See AAM, supra note 4, at 6.
\item \textsuperscript{17} CONG. BUDGET OFF., RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 6 (2021), https://www.cbo.gov/system/files/2021-04/57025-Rx-RnD.pdf. Supplemental data show that the average number of BLA approvals per year from 2015–2019 was 12.0, compared to an average of 32.0 new molecular entities per year. Data Underlying Figures and Tables, Supplemental Datasheet attached to Research and Development in the
approximately 43% of United States spending on pharmaceuticals. Responding to the rapid growth and accelerating costs of biologics, the Biologics Price Competition and Innovation Act (BPCIA) of 2010 established a process for the development and approval of follow-on biologics, more commonly known as biosimilars. In an effort to address several ongoing regulatory challenges, the FDA released its Biosimilars Action Plan in July 2018.

Similar to small-molecule generics, biosimilars can partially rely on clinical data from the innovator product but are also required to submit new data confirming that biosimilar products have “no clinically meaningful differences” from the original biologic. Although the United States has seen an increase in biosimilar development and approval over the last several years, the biosimilar marketplace has been slow to produce robust cost savings, generating $8 billion in savings in 2020; by 2025, spending on biosimilars is estimated to reach $133 billion.

This manuscript takes the following format: (1) a detailed explanation of the various challenges to generic competition in the combination product space; (2) a description and experience

---


21. Id. at 5, n.5.


23. See Mike Z. Zhai, Ameet Sarpatwari & Aaron S. Kesselheim, Why Are Biosimilars Not Living Up to Their Promise in the US?, 21 AMA J. ETHICS 668, 673 (2019) (advocating for greater biosimilar competition though they have not yet yielded the predicted cost savings); see also Ameet Sarpatwari, Rachel Barenie, Gregory Curlman, Jonathan J. Darrow & Aaron S. Kesselheim, The US Biosimilar Market: Stunted Growth and Possible Reforms, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 92, 94–95 (2018) (showing that biosimilars have, to date, only produced modest cost-savings).

24. See AAM, supra note 4, at 6; see also IQVIA INST., supra note 18, at 16.
to date of the FDA’s 505(b)(2) NDA and “complex generic” ANDA pathways as they pertain to combination products; (3) a series of case studies (with data) that provide real-world perspective to these market inefficiencies; and (4) proposed solutions for Congress, the FDA, and other key stakeholders as they attempt to address the high cost of prescription medications in the United States, including expensive combination products.

II. DRUG PRICING IN THE UNITED STATES

A. DRUGS ARE PRICED AT WHATEVER THE MARKET WILL BEAR

When a new drug is approved by the Food and Drug Administration, its list price is determined solely by the manufacturer. In spite of federal funding for the development of most new drug products, federal payers generally have little input into whether to cover a drug and at what price. The Centers for Medicare and Medicaid Services (CMS) can open a National Coverage Determination analysis to decide whether—and under what circumstances—to cover a new product, though these proceedings are relatively rare. Additionally, there are several statutorily defined categories for which federal coverage is required. Finally, the federal government is prohibited by


27. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE PRESCRIPTION DRUG BENEFIT MANUAL CHAPTER 6, Sec. 30.2.5; see also Policy Proposal: Revising Medicare’s Protected Classes Policy, THE PEW CHARITABLE TRUSTS (Mar. 7, 2018), https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2018/03/policy-proposal-revising-medicare’s-protected-classes-policy (explaining which drugs Medicare Part D plans are required to cover under federal statute).
statute from negotiating prices for Medicare Part B and Part D.

Drug price increases also go largely unchecked. In some cases, political uproar temporarily slows such increases, but the price rarely falls during the monopoly period. In fact, when drug price increases came under public scrutiny, manufacturers lauded their “single-digit price increase pledges,” even though many such increases were 9.9%. Generic drug prices can also rise dramatically, especially in situations where there are three or fewer manufacturers. Disgraced former pharmaceutical company CEO Martin Shkreli made such price hikes famous, leading to an investigation into sudden generic drug price increases by the United States Senate Special Committee on Aging.

Unlike the common pharmaceutical company narrative that high drug prices are meant to recoup the costs of research and development, some have characterized the industry’s staunch opposition to drug pricing legislation as “cry[ing] Innovation Wolf”; that is, any proposal to reign in drug prices is synonymous with bringing pharmaceutical innovation to a screeching halt. In reality, research and development

29. PDP Regions; Submission of Bids; Plan Approval, 42 U.S.C. § 1395w-111(i) (2021). This is commonly referred to as the Medicare Part D “non-interference clause.”
34. Id.
expenditures bear no relation to pricing of pharmaceuticals,35 and large pharmaceutical companies are seldom the ones responsible for generating innovative new drugs.36 Product life cycle management, including patent evergreening, is often considered part of research and development expenditures but is less about meaningful, patient-centered innovation and more about the preservation of a revenue stream for lucrative products.37 In response to legislative proposals and Congressional hearings, pharmaceutical companies and industry lobbying groups have significantly increased campaign contributions to politicians, aimed at thwarting drug pricing reforms.38

B. PATIENTS STRUGGLE TO AFFORD MEDICATIONS

A 2018 GoodRx survey found “that a full one-third of Americans have trouble paying for their medication—forcing them to borrow money, skip out on food or housing, or even not fill their prescriptions altogether because of the expense.”39 And a 2019 Kaiser Family Foundation survey noted that, as a result of high drug prices, nearly three in ten adults do not take their medications as prescribed.40 The most common responses were

35. See, e.g., Merrill Goozner, Drug Prices Are Unrelated to Research and Development Costs, HARV. HEALTH POLY REV. (Dec. 22, 2016), http://www.hhpronline.org/articles/2016/12/21/drug-prices-are-unrelated-to-research-and-development-costs (denying that pharmaceutical research and development costs are responsible for the high price of prescription drugs).


failure to fill prescriptions, patient-driven substitution for cheaper over-the-counter medications, cutting pills in half, or skipping or rationing doses. A 2021 IQVIA Institute report noted that “Patients were prescribed 55 million new therapy prescriptions by their doctors, which they abandoned at the pharmacy in 2020, about 9% of the total prescribed on average, with increasing frequency as costs rise.” Cost affects adherence to medication regimens: “[a]pproximately one in five new prescriptions are never filled, and among those filled, approximately 50% are taken incorrectly, particularly with regard to timing, dosage, frequency, and duration.” Finally, and perhaps most importantly, this practice is not benign; “nonadherence is associated with higher rates of hospital admissions, suboptimal health outcomes, increased morbidity and mortality, and increased health care costs.”

III. COMBINATION PRODUCTS

As pharmaceuticals became increasingly complex, particularly with regard to route of administration, manufacturers developed solutions aimed at improving patient experience. Many biologics cannot be taken orally, as the gastrointestinal tract poses several barriers to systemic absorption; such medications must therefore be infused or

41. Id.
43. Andrea B. Neiman et al., CDC Grand Rounds: Improving Medication Adherence for Chronic Disease Management – Innovations and Opportunities, CTRS. FOR DISEASE CONTROL & PREVENTION: MORBIDITY AND MORTALITY WEEKLY REPORT (Nov. 17, 2017), https://www.cdc.gov/mmwr/volumes/66/wr/mm6645a2.htm (citing Lars Osterberg & Terrence Blaschke, Adherence to Medication, 353 NEW ENG. J. MED. 487 (2005)).
44. Id. (citing M. Robin DiMatteo, Variations in Patients’ Adherence to Medical Recommendations: A Quantitative Review of 50 Years of Research, 42 MED. CARE 200 (2004)).
45. Julia Mantaj & Driton Vlasisliu, Recent Advances in the Oral Delivery of Biologics, THE PHARMACEUTICAL J. (Jan. 10, 2020), https://pharmaceutical-journal.com/article/research/recent-advances-in-the-oral-delivery-of-biologics (identifying “barriers” such as the environment of the gastrointestinal tract, including highly acidic stomach contents while noting that larger molecules like antibodies cannot pass across the intestinal mucosa the way their small-
injected. In other cases, such as for certain oncology drugs, self-administration is not feasible, requiring the medications to be delivered at designated infusion centers. Small-molecule drugs like naloxone and epinephrine are often administered via devices in a manner that allows for immediate pharmacologic activity in life-threatening situations. Some of these products have detailed instructions for use: the EpiPen is a multicolored device with instructions clearly written on the packaging, and Evzio is a pocket-sized device that reads directions aloud in English, much like an automated external defibrillator (AED).

Innovations that allow such medications to be administered safely and efficiently at home reduce health care expenditures. Combination products can also improve patient safety and adherence. For instance, medications like insulin would historically be dispensed to patients as a vial with a set of syringes and needles. In some cases, an individual would need to reconstitute the drug from powder and draw up appropriate aliquots for each administration; in others, a specified number of individual syringes would come with pre-filled quantities of the drug for single use. Improvements in device technology have automated much of the process. Now, in place of a messy kit or bulky set of single-use syringes, a single “pen” may contain

molecule counterparts can); see also Ester Caffarel-Salvador et al., Oral Delivery of Biologics Using Drug-Device Combinations, 36 CURRENT OP. PHARMACOLOGY 8 (2017) (examining how orally administered devices could allow clinicians to “engineer around” the barriers of the GI tract).

46. See infra Case Study 3. Naloxone, a strong opioid antagonist initially developed as an intravenous medication, was reformulated to an intranasal version for broader use, including emergency response and bystander rescue, during overdoses due to opioid toxicity. Id. Epinephrine can be administered via an intramuscular autoinjector, most commonly via the EpiPen autoinjector. How EpiPen® Works, EPI PEN, https://www.epipen.ca/how-epipen-works (last accessed Dec. 11, 2021).

47. See, e.g., Jeffrey S. Farroni, Leonard Zwelling, Jorge Cortes & Hagop Kantarjian, Saving Medicare through Patient-Centered Changes – The Case of Injectables, 368 NEW ENG. J. MED. 1572 (2013) (arguing that the expansion of medical insurance coverage to encompass self-administered injectable drugs will reduce health care costs).


49. Id. at 1253 (explaining that pre-filled syringes are extremely common in the inpatient setting but are now seldom used in the outpatient setting).
enough doses to last days to weeks, with simplified techniques for administration that reduce user error.\textsuperscript{50}

As manufacturers have innovated to develop products for self-administration, they have done so by developing their own proprietary medical devices. The regulatory process can be summarized as follows:

Combination products—whether a drug and device, a drug and biological product, a biological product and device, or a product combining all 3—are currently overseen by the Office of Combination Products (OCP), which assigns investigational combinations to an FDA center based on the component producing the combination’s primary mode of action. Combinations deemed to be primarily drugs are assigned to the Center of Drug Evaluation and Research (CDER), biologics to the Center for Biologics Evaluation and Research (CBER), and devices to the Center for Devices and Radiological Health (CDRH).\textsuperscript{51}

Because officials from CDER and CBER may not have the same level of expertise as CDRH officials when it comes to reviewing medical devices, combination products reviewed by CDER or CBER alone may not undergo a sufficiently thorough review of the product’s device component.\textsuperscript{52} That said, intercenter consultations are common for such products.\textsuperscript{53}

A. LISTING OF PATENTS IN THE FDA’S “ORANGE BOOK”

In the late 1970s, the FDA acknowledged a trend toward state repeal of anti-substitution legislation so long as substitute

\textsuperscript{50} Id. at 1254–56 (describing advancements in insulin delivery devices).
\textsuperscript{51} Bo Wang & Aaron S. Kesselheim, Promoting Therapeutic Innovation: What Do We Do About Drug-Device Combinations?, 315 J. AM. MED. ASS’N 857 (2016). This paper will focus on combinations deemed to be primarily drugs and biologics. Combinations deemed to be primarily devices, such as drug-eluting cardiovascular stents and insulin infusion pumps, are outside the scope of this paper.
\textsuperscript{52} For a drug-device combination that operates primarily as a device, like a drug-eluting vascular stent, CDRH may expend more effort into reviewing the structure and function of the device. For a drug-device combination like an insulin pen, CBER may not spend adequate time evaluating the device component. See Jordan Paradise, Insulin Federalism, 27 B.U. J. SCI. & TECH. L. 118, 170 (2021) (outlining problems that arise from the current legal and regulatory framework surrounding biologic products).
\textsuperscript{53} U.S. FOOD & DRUG ADMIN., INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH AND THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (1991) (exhibiting an agreement between the CDER and CDRH to regulate certain products as devices and others as drugs).
drugs were limited to a specific list. In response to state requests that the FDA generate such a list, the agency created its first book of “Approved Prescription Drug Products with Therapeutic Equivalence Evaluations” in October 1980. The book became colloquially known as the “Orange Book” due to its bright orange cover and initial publication on October 31, 1980, coinciding with Halloween.

Initially, the Orange Book identified products with the same active ingredient and the same strength, dose, and route of administration. Upon being codified into law via the Hatch-Waxman Amendments, all holders of approved NDAs were required to file “the patent number and expiration date of any effective patents which claim the drug or a method of using such drug” for listing in the Orange Book. This included drug composition and formulation patents for all new and existing NDAs.

Because there were many off-patent drugs with few to no competitors, the Hatch-Waxman Act also created the ANDA pathway to expedite review and approval of generics, which could then be listed in the Orange Book and subjected to state substitution laws, thereby limiting brand-name market dominance and increasing competition.

---

55. Id.
B. PRODUCT LIFECYCLE MANAGEMENT

After drugs are approved, pharmaceutical companies often engage in the practice of product lifecycle management, a process by which additional patents are obtained on a product in order to extend patent protection and forestall generic entry.61

Upon the passage of the Hatch-Waxman Act of 1984, it quickly became clear that patents were the key to extending market exclusivity of lucrative drug products in the United States. An unforeseen flaw in the Orange Book derives from the process by which the FDA lists patents covering a particular drug.62 Later-expiring patents delay generic competition because Paragraph IV certifications and patent settlements often leave those patents in force. For primary patents, which cover the chemical compound, patent challenges often result in settlement or affirmation of patent validity.

C. POSTMARKET RESEARCH AND DEVELOPMENT

Empirical analyses of marketed drugs confirm that the postmarket period for many marketed drugs consists of follow-on research and development closely tied to product lifecycle management.63 One study evaluating postapproval trials for the drug pregabalin (Lyrica) identified 238 trials for nonapproved


indications, many of which were exploratory and intended to generate supplemental uses for the drug. Many of these studies were inconclusive, but such studies can still drive off-label use, even if data supporting those uses is limited.

Importantly, obtaining a “method of use” patent for a particular product may pose a barrier to generic entry, even if that use is not FDA-approved. That is, a postmarket study could be insufficient to justify approval of a supplemental indication from the FDA, but might be enough for the United States Patent and Trademark Office (USPTO) to issue a “method of use” patent. Several thousand patients are enrolled in these exploratory trials, with few positive outcomes and multiple replicated negative studies, suggesting that inefficiencies in postmarket research and development have real implications for patients. Risks may outweigh benefits in many cases, which wastes resources while unnecessarily exposing patients to harm.

## D. Evergreening: Secondary and Tertiary Patents

This highlights a second important aspect of product lifecycle management: evergreening. The concept is aptly

---

64. See generally Federico et al., supra note 63 (outlining the study).


66. See Timothy R. Holbrook, Method Patent Exceptionalism, 102 IOWA L. REV. 1001, 1005 (2017) (“Such ‘method of use’ patents can be quite important: if an inventor finds a new use for an old drug, she can get a patent on the new method for using the drug even though she cannot get a patent on the drug itself.”).


69. Id. at 15.

70. ROBIN FELDMAN, RETHINKING PATENT LAW 170–78 (2012); see also Carl Shapiro, Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard-Setting, in 1 INNOVATION POLICY AND THE ECONOMY 119 (Adam B. Jaffe, Josh Lerner & Scott Stern eds., 2001) (explaining the difficulty of
defined by Rebecca Eisenberg as follows: pharmaceutical manufacturers adopt “evergreening strategies that add new patents to their quivers as old ones expire,” and in doing so, “prolong their effective periods of patent protection.”

By adding patents or exclusivities to a product’s portfolio, manufacturers can effectively dissuade generic competition by implementing structural barriers to market entry. An analysis of pharmaceutical patent evergreening from 2005 to 2015 revealed that 78% of new patents listed in the Orange Book covered existing drugs, with over 70% of the top 100 bestselling drugs obtaining at least one extension of market exclusivity.

1. Secondary Patents

Secondary patents cover aspects of a drug such as its formulation, method of use, or minor structural modifications such as enantiomers, prodrugs, or salts. Unlike primary patents on the new chemical entity or new molecular entity, which are generally filed and issued prior to FDA approval, many secondary patents are filed and issued after approval. Even though secondary patents are thought to be more vulnerable to invalidation in patent challenges, they are commonly invoked to delay market entry of generics. One study of the HIV medications ritonavir [Norvir] and lopinavir/ritonavir [Kaletra] identified 108 patents which would have delayed generic competition until 2028, a full thirty-nine years navigating the “patent thicket” of overlapping existing patent rights when developing new products).


73. Feldman, supra note 72, at 596.

74. Amy Kapczynski, Chan Park & Bhaven Sampat, Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of “Secondary” Pharmaceutical Patents, 7 PLOS ONE 1, 3 (2012); see also Kesselheim, Sinha, Avorn & Sarpatwari, supra note 65, at 439.

75. Kapczynski et al., supra note 74, at 5.

76. Kapczynski et al., supra note 74, at 2.
years after the first patents on ritonavir were filed. Though generic versions of ritonavir are now available, patents for three other combination medications containing ritonavir expire as late as 2035.

2. Tertiary Patents

Recently, scholars have described a new category of pharmaceutical patents for combination products: patents covering the drug delivery device component. One study found that these so-called “tertiary patents” extend patent protection by a median of 4.7 years; for forty-four of the forty-nine drugs studied, tertiary patents were the last to expire. The number of drug-device products listed in the FDA’s Orange Book nearly doubled from 2005 to 2016, with a concomitant increase in tertiary patents from sixty-one to 478. Tertiary patents have become increasingly important to patent evergreening strategies; in 2016, one in four combination products had only tertiary patents remaining in the Orange Book. These tertiary patents expired later than other patent types and, had they not been listed in the Orange Book, would have allowed generics to enter the market a median of 3.4 years sooner.

78. U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (41st ed. 2021) [hereinafter ORANGE BOOK] (providing patent data for Viekira Pak, Viekira XR, and Technivie).
81. Beall & Kesselheim, supra note 79, at 142.
82. Beall & Kesselheim, supra note 79, at 142–43 (identifying three major factors contributing to an increase in tertiary patents: (1) tertiary patents growing role in combinatorial product patent portfolios, (2) a growing subset of combinatorial products filing tertiary patents, and (3) the same products accruing tertiary patents over time).
83. Beall & Kesselheim, supra note 79, at 142–43.
filed tertiary patents suggest that manufacturers continue to innovate the device even after the product has entered the market, with several redesigned devices flagged for recall by the FDA as having a “defective delivery system.”\textsuperscript{84} Because tertiary patents cover mechanical aspects of the device, they may be less prone to invalidation as compared to secondary patents, which cover variants of a drug that may later be found to be non-novel or obvious, such as an enantiomer or salt of a drug.\textsuperscript{85}

E. COST OF DRUG-DEVICE COMBINATION PRODUCTS

Of the top twenty medicines by non-discounted spending in 2019, seven have associated devices.\textsuperscript{86} Combined, these seven drugs alone have gross sales of $208.9 billion from 2015 to 2019.\textsuperscript{87}

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>$10.1b</td>
<td>$13.5b</td>
<td>$16.3b</td>
<td>$18.4b</td>
<td>$21.4b</td>
<td>$79.7b</td>
</tr>
<tr>
<td>Enbrel</td>
<td>$7.2b</td>
<td>$7.6b</td>
<td>$7.9b</td>
<td>$8.0b</td>
<td>$8.1b</td>
<td>$38.8b</td>
</tr>
<tr>
<td>Stelara</td>
<td>$2.0b</td>
<td>$2.6b</td>
<td>$3.7b</td>
<td>$5.0b</td>
<td>$6.6b</td>
<td>$19.9b</td>
</tr>
<tr>
<td>Trulicity</td>
<td>$0.3b</td>
<td>$1.2b</td>
<td>$2.7b</td>
<td>$4.5b</td>
<td>$6.5b</td>
<td>$15.2b</td>
</tr>
<tr>
<td>Lantus Solostar</td>
<td>$5.8b</td>
<td>$5.5b</td>
<td>$4.8b</td>
<td>$4.3b</td>
<td>$4.3b</td>
<td>$24.7b</td>
</tr>
<tr>
<td>Symbicort</td>
<td>$2.7b</td>
<td>$3.0b</td>
<td>$3.1b</td>
<td>$3.5b</td>
<td>$3.9b</td>
<td>$16.2b</td>
</tr>
<tr>
<td>Victoza 3-Pak</td>
<td>$2.0b</td>
<td>$2.4b</td>
<td>$2.9b</td>
<td>$3.5b</td>
<td>$3.6b</td>
<td>$14.4b</td>
</tr>
</tbody>
</table>

84. Beall & Kesselheim, supra note 79, at 144.
87. Infra Table 1.
88. IQVIA INST. FOR HUM. DATA SCI., supra note 86.
F. COMPETITION AND DRUG-DEVICE COMBINATIONS

In many ways, the Hatch-Waxman Act can be characterized as a success. Prior to the law taking effect, generics represented 19% of all drugs dispensed, and only 35% of off-patent drugs faced generic competition. By 2020, generics represented nine out of every ten prescriptions and accounted for only 18.1% of prescription drug spending. Generics saved consumers and payers $338 billion in 2020.

Brand-brand competition rarely results in substantial savings to consumers. In fact, price increases of many competitor products have appeared to rise in lock-step, raising the specter of anti-competitive behavior. Manufacturers often argue that they increase prices in order to compete with competitors for preferred tiering on major pharmacy benefit manager (PBM) formularies; rebates are often calculated as a percentage of the list price, meaning that list price increases are the clearest path to PBMs.

In the combination product space, personal preference and familiarity with use may make brand loyalty more common.}


90. See AAM, supra note 4, at 6. The remaining 10% of prescriptions are for brand-name products, which account for a whopping 81.9% of prescription drug spending. Id.

91. AAM, supra note 4, at 6.

92. See, e.g., Ameet Sarpatwari, Jonathan DiBello, Marie Zakarian, Mehdi Najafzadeh & Aaron S. Kesselheim, Competition and Price Among Brand-Name Drugs in the Same Class: A Systematic Review of the Evidence, PLOS MED., July 30, 2019, https://doi.org/10.1371/journal.pmed.1002872 (finding that brand-brand competition “will likely not result in lower drug prices absent structural reforms”).


95. Jing Luo & Aaron S. Kesselheim, Evolution of Insulin Patents and Market Exclusivities in the USA, 3 LANCET DIABETES & ENDOCRINOLOGY 835,
Physicians are often reluctant to switch patients to other products because of usability concerns. In generic small-molecule drug markets, it is fairly common to find ten or more generic competitors. A study found that 63% of novel small-molecule drugs in encapsulated or tablet form have four or more generic approvals. Blockbuster combination products, however, rarely have the same degree of competition. Competition is even less likely for biologics—biosimilar-device combinations differ in both therapeutic and device components—which has driven some degree of skepticism among physicians and patients, mirroring the skepticism that once plagued small-molecule generics decades ago.

IV. GENERICS FOR COMBINATION PRODUCTS

Given that combination products are increasingly common but the marketplace for generics remains small, the FDA has

837 (2015) (identifying patents covering insulin products, including formulation and pen-device patents).
96. See Louise Heron et al., Perceptions of Usability and Design for Prefilled Insulin Delivery Devices for Patients With Type 2 Diabetes, 26 DIABETES SPECTRUM 16 (2013) (“Healthcare Practitioners] understand patient preferences and therefore may be able to adjust their prescribing decisions to meet these preferences.”); see also Jerome S. Fischer et al., United States Patient Preference and Usability for the New Disposable Insulin Device Solostar® Versus Other Disposable Pens, 2 J. DIABETES SCI. & TECH. 1157 (2008) (comparing patient preference and usability of various insulin injection devices).
97. See Ravi Gupta, Aaron S. Kesselheim, Nicholas Downing, Jeremy Greene & Joseph S. Ross, Generic Drug Approvals Since the 1984 Hatch-Waxman Act, 176 J. AM. MED. ASS’N INTERNAL MED. 1391, 1392 (2016) (explaining that, for drugs with at least a single generic competitor, the median number of generic competitors is seven; then noting that 17% of all drugs eligible for generic competition had no generic competition). For an analysis of mitigating factors that contribute to increasing generic drug prices, see Tessema et al., supra note 31.
98. See ALEX BRILL, POTENTIAL SAVINGS FROM ACCELERATING US APPROVAL OF COMPLEX GENERICS (2021), https://accessiblemed.org/sites/default/files/2021-02/Potential-Savings-Complex-Generics-Feb2021.pdf (defining complex generics as “copies of non-biologic medicines that have a complex molecular base, route of delivery, formulation, or dosage form; . . . a drug-device combination product; or [a product with] other particularly complex approval requirements.”); see Alford, supra note 1, at 478–79.
99. Zhai et al., supra note 23, at 671–72 (internal citations omitted) (citing a 2016 national survey where 55% of physicians “did not believe that biosimilars were safe and appropriate for use in patients” and a 2018 Citizen Petition to the FDA expressing doubt and confusion regarding the safety and efficacy of biosimilars).
prioritized the review and approval of complex generics—intended to compete with combination products—by offering guidance to industry for developing such products. The FDA placed an additional evidentiary requirement for complex generics; substantial duplication of the medical device. In particular, the FDA was concerned about the usability of medical device components of combination products: “the use of human factors and usability engineering . . . plays a key role in maximizing the likelihood that the device will be safe and effective for use by the intended users, for the intended uses, and for the intended use environments.” In doing so, the agency pointed to the need “to ensure that use-related hazards associated with the product are eliminated or mitigated to reduce patient adverse events and medication errors attributable to use-related errors.” In drafting this guidance, the FDA may have also considered statutory requirements of label equivalency with the brand-name product.

However well-intentioned, greater evidentiary requirements for complex generics have hindered competition in the combination products market because devices are often very difficult to replicate in practice. In fact, there are several complex generics that have been approved by regulatory agencies in Canada and Europe but not the United States, contributing to between $600 million and $1.7 billion annually in excess spending.


101. See infra Case Study 1.

102. FDA HUMAN FACTORS STUDIES, supra note 100, at 4.

103. Id. at 5.

104. See 21 C.F.R. § 314.94(a)(8)(iv) (2021) (requiring all differences in side-by-side comparisons, including Medication Guides, to be annotated and explained).

105. BRILL, supra note 98, at 3–4 (“Due to the inherent complexity of manufacturing these products, the expected number of generic competitors is generally one, two, or perhaps three.”).

106. BRILL, supra note 98, at 7 (noting that savings may have been realized had the FDA approved the ANDAs quicker).
Given the challenges associated with replicating a combination product’s medical device to an acceptable degree of specificity, many companies appear to have either abandoned the idea of pursuing an ANDA or shifted their development strategy toward the 505(b)(2) NDA pathway. Depending on the goals of pursuing a competitor product, each pathway has its advantages and disadvantages.

A. INTERCHANGEABILITY AND AUTOMATIC SUBSTITUTION

Currently, there are two primary mechanisms by which manufacturers can develop competitor products with the same active ingredients as marketed drug-device combinations. The first is the approval of a “complex generic” via the traditional ANDA, the pathway by which generic small-molecule drugs are approved.107 A second is via the 505(b)(2) new drug application pathway, which allows a rival company to rely on published data from marketed products as part of its application.108 In some circumstances, the 505(b)(2) pathway may be a particularly appealing alternative to an ANDA, because instead of being required to replicate the brand-name device to a high degree of specificity, the generic manufacturer could simply develop its own drug delivery device or repurpose existing technology controlled by the manufacturer, such as comparable devices. Instead of generating an interchangeable complex generic via the ANDA pathway, the 505(b)(2) product can effectively be thought of as a brand-name “generic.” Often accompanied by its own market exclusivity period, the product may need to be heavily promoted by the manufacturer in order to gain market share. For this reason, ANDAs—and not 505(b)(2)s—are the most plausible route to lower drug prices, because generic small-molecule drugs can be automatically substituted at the pharmacy level in all fifty states, and no distinction is made in most cases for drug-device combinations.109

108. 21 U.S.C. § 355(b)(2) (2021) (describing the (b)(2) application as “an application submitted under [Section 505(b)(1)"").
Established under the Hatch-Waxman Act of 1984, the 505(b)(2) NDA pathway allows applicants to rely in part on data submitted for a previous NDA. The idea was to allow drug companies to improve versions of existing drugs (i.e., updated formulations or new uses) through a separate market incentive. In fact, the 505(b)(2) pathway has increasingly been utilized for approval over time; by 2004, there were more approved applications via the 505(b)(2) pathway than the traditional 505(b)(1) pathway for new molecular entities, a trend that has continued to this day.

A. Effect on Competition and Price

Depending on the circumstances, there may be commercial advantages to pursuing a 505(b)(2) application. One pharmaceutical consulting firm describes the 505(b)(2) pathway as “a [potentially] much less expensive and much faster route to approval, compared to a traditional development path.”

There is also a lower burden on the manufacturer to generate new data for the regulatory submission, particularly data from clinical trials. All applications rely on data from a previously approved product (often referred to as the “reference listed drug” or RLD), but in lieu of additional studies, many will obtain data from other sources, such as peer-reviewed scientific journals. This means fewer clinical studies, less time to approval, and lower risk of rejection given reliance on data from approved products. Finally, many of these products receive the

111. Jonathan J. Darrow, Mengdong He & Kristina Stefanini, The 505(b)(2) Drug Approval Pathway, 74 FOOD & DRUG L.J. 403, 405 fig. 1, 413 fig. 9 (2019). The 505(b)(2) pathway is most commonly used for FDA Classification Codes 3 (New Dosage Form), 4 (New Combination), and 5 (New Formulation or New Manufacturer). Id. at 406.
same Hatch-Waxman regulatory exclusivity periods as 505(b)(1)-approved drugs.\textsuperscript{114}

Despite these benefits, there are also drawbacks. FDA user fees are higher for brand-name products than generics.\textsuperscript{115} Similarly, there is less market penetration because 505(b)(2)-approved products do not immediately receive interchangeability designations, which would allow for automatic substitution at the pharmacy.\textsuperscript{116} Successful complex generic ANDAs receive AB ratings in the Orange Book, whereas 505(b)(2)-approved combination products generally receive a BX rating.\textsuperscript{117}

With these considerations in mind, why might a manufacturer choose the 505(b)(2) pathway? Instead of being required to replicate a brand manufacturer’s device to the degree of specificity the FDA requires for complex generics,\textsuperscript{118} the manufacturer can simply develop work-around devices once active ingredient patents expire. This saves time and expense associated with reverse engineering and serial testing of devices—including human factors studies\textsuperscript{119}—and allows for the

---

\textsuperscript{114} See Darrow et al., supra note 111, at 410 (42% (231 of 553) of 505(b)(2) applications in the study sample received some form of regulatory exclusivity).

\textsuperscript{115} See Mezher, supra note 13 (in 2021, NDAs not requiring clinical data cost $1.4 million in user fees, whereas ANDAs cost just under $200,000).

\textsuperscript{116} See infra Case Study 1. Another classic example is EpiPen. See, e.g., Lydia Ramsey Pflanzer & Andy Kiersz, EpiPen’s Skyrocketing Prices Can’t Be Blamed on No Competition, BUSINESS INSIDER (Sept. 13, 2016), https://www.businessinsider.com/epipen-prescriptions-auvi-q-adrenaclick-2016-9 (noting that competitors Twinject, Adrenaclick, and Auvi-Q failed to gain market share over the years). All three were approved via the 505(b)(2) pathway. Id.

\textsuperscript{117} See Norris & Crose, supra note 113. One interesting exception to this rule is the 505(b)(2)-approved testosterone gel product marketed by Perrigo Company plc. Despite opposition from AbbVie, the maker of brand-name AndroGel, the Perrigo product was granted an AB rating. FDA Grants AB Rating to 505B2 NDA Generic, PHARM. DEV. GRP. (Aug. 1, 2014), https://pharmdevgroup.com/fda-grants-ab-rating-505b2-nda-generic/ [hereinafter PHARM. DEV. GRP.]. A 505(b)(2) testosterone gel product from Teva was granted a BX rating and the company ultimately decided against marketing it. Id.; see also FTC v. AbbVie Inc., No. 2:14-cv-05151-HB (E.D. Pa. 2018) (discussing these facts in the context of a court ruling on an FTC suit against AbbVie).


\textsuperscript{119} See generally FDA HUMAN FACTORS STUDIES, supra note 100 ("This document provides guidance to industry and FDA Staff on the underlying
use or repurposing of devices for which the generic manufacturer may have separate intellectual property protections. These associated time and cost savings may make the 505(b)(2) pathway far more lucrative by decreasing barriers to market entry.  

VI. THE FDA AND COMPLEX GENERICS: 3 CASE STUDIES

The challenge of developing generic combination products has been a recent priority for the FDA: in October 2017, the agency announced an initiative to improve the ANDA submission process for complex generic drugs, intended to diminish regulatory uncertainty that may otherwise deter generic manufacturers from attempting to enter the market. In 2020, the FDA finalized guidance for its pre-ANDA program, intended to “clarify regulatory expectations for prospective applicants early in product development, assist applicants to develop more complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for [complex products].”

Meeting types include product development meetings, pre-submission meetings, and mid-review-cycle meetings. As FDA Commissioner Scott Gottlieb noted in 2017, “because brand-name versions of complex drug products are often higher-priced than many other brand name drugs, any steps we can take to encourage the development of generic competitors to complex drugs will have an outsized impact on access, and prices.”

This section will consist of three case studies: (1) fluticasone/salmeterol [Advair]; (2) adalimumab [Humira]; and

principles of human factors (HF) studies during the development of combination products . . . ."

120. The epinephrine entry in the 2021 Orange Book is demonstrative. See ORANGE BOOK, supra note 78, at 3–363 (showing Adrenaclick and Auvi-Q have BX ratings while the newer ANDA-approved generic epinephrine autoinjector from Teva has an AB rating).

121. Gottlieb, supra note 100.


123. Id. at 3–5.

124. Gottlieb, supra note 100.
(3) naloxone [Narcan and Evzio]. Other important examples, like the epinephrine autoinjector [EpiPen] and insulin devices, tell similar stories but have been covered in detail elsewhere.

A. CASE STUDY 1: FLUTICASONE/SALMETEROL [ADVAIR DISKUS]

Indicated for severe asthma and chronic obstructive pulmonary disease, fluticasone propionate/salmeterol xinafoate [Advair Diskus] is a brand-name inhaled combination corticosteroid and long-acting beta-agonist. The product was initially approved by the FDA in August 2000 and awarded three years of regulatory exclusivity as a new combination. The primary patent for fluticasone was issued in 1982; the primary patents for salmeterol were issued between 1991 and 1993.

The last of these primary patents was set to expire in August 2008, but a series of patents on the Diskus® drug delivery device extended patent exclusivity—and therefore, the product’s market monopoly—until 2016. This occurred through the procurement of tertiary patents covering the combination product’s delivery device and listing of those


126. See generally Luo & Kesselheim, supra note 95 (explaining how patents impact access to insulin in the United States).


128. Approval Letter 21-077, supra note 118.


130. See Beall et al., supra note 80, at 4 tbl. 1 (showing patent protection extensions for the Diskus drug delivery device granted through August 2016).
patents in the Orange Book. In fact, the manufacturer (GSK) applied these device patents to other combination products by packaging other drugs with delivery devices that differed only in terms of color: fluticasone propionate [Flovent Diskus], and salmeterol xinafoate [Serevent].

The challenges associated with developing complex generics for Advair were anticipated by the FDA early on. In response to a perceived lack of clarity around the ANDA approval process for Advair generics, the FDA issued a draft guidance in February 2013—three years before anticipated expiration of market exclusivity—recommending four additional studies for ANDA approval and delineating criteria for each. The FDA sought to ensure that competitor products would be “qualitatively . . . and quantitatively . . . the same” as the Advair Diskus with respect to inactive ingredients and device characteristics:

- “Passive (breath-actuated) device
- Pre-metered multi-dose format
- 60 doses
- External operating procedures consisting of (1) Open, (2) Click, (3) Inhale, and (4) Close
- Similar size and shape to the [reference] product
- Comparable device resistance to the [reference] product
- Dose counter”

In February 2016, a second draft guidance addressed complex generic product design more broadly, focusing on

131. Nine additional patents, all titled “Inhalation device,” were filed between 1995 and 2005. The last of these, covering the “medicament pack” containing powdered fluticasone and salmeterol, expired in 2016. U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 949–50 (30th ed. 2010).
132. Id. at 945–46, 1038. Identical in function and operation, the only difference is the color of the devices. The Advair Diskus is purple, the Flovent Diskus is orange, and the Serevent Diskus is green. See D. McDaniel & K. Schleich, Treating Asthma and COPD: Chart of Inhaled Medications, U. IOWA, https://www.healthcare.uiowa.edu/familymedicine/fpinfo/Docs/Inhaler%20chart%20pdf2.pdf (providing images of the mentioned devices and their respective colors).
133. U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE ON FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE (2013).
134. Id.
135. Id.
human factors studies—studies intended to evaluate whether patients can use the complex generic device properly without serious problems or use errors.\textsuperscript{136}

The Advair Diskus is a blockbuster drug with over $100 billion in lifetime sales,\textsuperscript{137} yet there are only three market competitors containing fluticasone and salmeterol in 2021: products made by Mylan, Hikma, and Teva.\textsuperscript{138}

1. Mylan’s Wixela Inhub

Soon after the final Diskus device patent expired in early 2016, Mylan submitted its ANDA for the Wixela Inhub.\textsuperscript{139} Before the FDA could make its determination on Mylan’s application, Sandoz—a rival manufacturer also seeking to produce a complex generic of Advair—submitted a Citizen Petition in October 2016 encouraging the FDA to reject all pending Advair Diskus ANDA applications until the agency could clarify “inadequacies” in its 2013 Advair draft guidance.\textsuperscript{140} Recent studies have demonstrated that Citizen Petitions from manufacturers often delay approval of competitor products; Sandoz’ petition may have been intended to delay Mylan’s approval until it could get its own generic fluticasone/salmeterol product to market.\textsuperscript{141} The FDA denied the Sandoz petition in March 2017 and rejected Mylan’s ANDA later that month, issuing the company a Complete Response Letter (CRL).\textsuperscript{142}

\textsuperscript{136} See FDA HUMAN FACTORS STUDIES, supra note 100.
\textsuperscript{137} James Paton, Glaxo’s Advair Is the $100 Billion Asthma Drug That Won’t Die, BLOOMBERG (May 4, 2018), https://www.bloombergquint.com/business/glaxo-s-advair-is-the-100-billion-asthma-drug-that-won-t-die.
\textsuperscript{138} Search Results from Drugs@FDA: FDA-Approved Drugs, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (search “fluticasone” and “salmeterol”).
\textsuperscript{141} See generally Michael A. Carrier & Carl Minniti, Citizen Petitions: Long, Late-Filed, and At-Last Denied, 66 AM. U. L. REV. 305 (2016) (exploring how brand firms can use Citizen Petitions to delay market entry of generic medicines, resulting in higher prices to consumers).
\textsuperscript{142} See FDA Declines to Approve Mylan’s Generic of GSK’s Advair For Now, REUTERS (Mar. 29, 2017), https://www.reuters.com/article/us-mylan-fda-
FDA designated Mylan’s ANDA as requiring a major amendment, which results in delays associated with a revised application and FDA response. After Mylan’s ANDA received a second CRL from the FDA in January 2018, the Wixela Inhub was FDA-approved via the ANDA pathway in January 2019.

Three weeks into its launch, Mylan captured nearly one quarter of the market, and at a list price 70% lower than Advair.

More competition is on the way: Sandoz and Hikma have closely followed Mylan’s pursuit of a complex generic. Each company has similarly had ANDA submissions rejected by the FDA but have continued to pursue complex generics for fluticasone/salmeterol. Hikma’s product received FDA approval in December 2020, though Sandoz remains unsuccessful to date.

2. Teva’s AirDuo

In its pursuit of a competitor to the Advair Diskus, Teva took the alternative regulatory approach, receiving approval through the 505(b)(2) pathway for its own fluticasone/salmeterol product (AirDuo® Respiclick) in January 2017. Teva also produced an authorized generic (a product identical to the

advair/fda-declines-to-approve-mylans-generic-of-gsks-advair-for-now-idUSKBN1702LC (“Both analysts think it’ll be awhile before the GlaxoSmithKline respiratory knockoff does win approval, especially if Mylan has additional work to do.”).


AirDuo but with a generic label), and in response, GSK launched its own authorized generic of Advair, manufactured by Prasco Laboratories; both products launched in April 2017. Since Teva did not pursue an ANDA approval, neither AirDuo nor its authorized generic can be automatically substituted by a pharmacy receiving a prescription for “Advair Diskus.” Market share therefore depends on astute prescribers to write prescriptions for “Teva AirDuo,” requiring Teva to aggressively promote its product to prescribers, payers, and patients in order to gain market share.

3. GSK’s Product Hop: Advair HFA

In the meantime, GSK sought to protect a portion of its revenues and market share for the Advair Diskus by obtaining approval for a new Advair product, the Advair HFA inhaler. The Advair HFA product represents a product hop, characterized by FDA approval and market launch of a related product, generally with a later-expiring market exclusivity.


149. Teva Announces FDA Approval of AirDuo® Digihaler™ (fluticasone propionate 113 mcg and salmeterol 14 mcg) Inhalation Powder, TEVA PHARMACEUTICALS (July 15, 2019), https://www.tevapharm.com/news-and-media/latest-news/teva-announces-fda-approval-of-airduo-digihaler-fluticasone-propionate-113-mcg-and-salmeterol-14-mcg/ (describing the product as follows in their press release: “AirDuo® Digihaler™ contains built-in sensors that detect when the inhaler is used and measure inspiratory flow rates. This data is then sent to a companion mobile app using Bluetooth® Wireless Technology so that patients can review their data over time, and if desired, share it with their healthcare providers. Patients can also schedule reminders on their smartphone to take their AirDuo® Digihaler™ as prescribed”).

150. There was a push in the 1980s to eliminate chlorofluorocarbon (CFC) propellants from respirators for environmental concerns; the replacement propellant, hydrofluoroalkane (HFA), is now raising similar concerns. Sarah DeWeerdt, The Environmental Concerns Driving Another Inhaler Makeover, 581 NATURE 14 (2020). Product hops due to these changes have prolonged market exclusivity of respiratory devices for decades. See id. (describing the tension between striving for a smaller carbon footprint and maintaining patient access to needed devices).
period, in an effort to preserve market share of particularly lucrative branded products.\textsuperscript{151} With patents extending market exclusivity for Advair HFA until 2031, GSK has been strategically shifting market share from the Advair Diskus to the Advair HFA, corresponding to a soft switch.\textsuperscript{152} The latest-expiring patents for the Advair Diskus and the Advair HFA are both device patents; the Advair HFA patent covers the dose counter.\textsuperscript{153}

\textsuperscript{151} The most concerning of product hops are hard switches, which result when a manufacturer seeks to switch users to the new product before discontinuing the old product. More insidious but perhaps equally anticompetitive are soft switches, in which a manufacturer introduces a new variant of its drug product (usually with extended market exclusivity) and gradually switch patients over to that formulation before its flagship product loses exclusivity and faces generic competition. In the soft switch scenario, the flagship product is not discontinued prior to entry of generic competition, but promotion and marketing are often shifted toward prescribing of the new product.

\textsuperscript{152} See infra Figure 1.

Figure 1. Expiration of Orange Book-Listed Patents for Advair-Branded Fluticasone/Salmeterol Products

As generic entry has driven down Advair’s market share, GSK now offers drug coupons promoting a $10 monthly copay while encouraging patients to ask their physicians to prescribe brand-name Advair.\textsuperscript{155} On its main website, it also warns patients that pharmacies may switch them to a generic, asking the question, “Are you sure you’re getting the same medicine in the Diskus inhaler?”\textsuperscript{156} The website also explains that the product is “Available Two Ways,” recommending either the brand-name Diskus or its authorized generic, marketed as “the same medicine in the exact same Diskus inhaler.”\textsuperscript{157}

![Figure 2. Advair Website.\textsuperscript{158}](image)

The claims on the product website may have the effect of generating skepticism about complex generic competitors to Advair. Also, both the Advair Diskus and the authorized generic


\textsuperscript{156} Asthma and COPD treatment | Advair (fluticasone propionate and salmeterol), ADVAIR, https://www.advair.com (last accessed Aug. 27, 2021).

\textsuperscript{157} Id.

\textsuperscript{158} Id.
are purple; the product’s design, including color, seems intended to foster brand loyalty among physicians and patients.\textsuperscript{159}

4. Impact on Market Share

The Advair Diskus held considerable market share as late as 2019.\textsuperscript{160}

\textbf{Figure 3 (continued on next page). Medicaid and Medicare Part D Spending on Fluticasone/Salmeterol Combination Products.}\textsuperscript{161}

\textsuperscript{159} Just as AstraZeneca’s “purple pill” (first omeprazole [Prilosec], then esomeprazole [Nexium]) was intended to generate brand loyalty and may have generated skepticism of non-purple generic alternatives, the distinctive purple color of the Advair Diskus may also foster skepticism about complex generics like Mylan’s Wixela Inhub. See generally Ameet Sarpatwari & Aaron S. Kesselheim, \textit{The Case for Reforming Drug Naming: Should Brand Name Trademark Protections Expire upon Generic Entry?}, PLOS MED., Feb. 9, 2016 (discussing the merits of allowing generic drug products to adopt the name of their brand name counterpart); Jeremy A. Greene & Aaron S. Kesselheim, \textit{Why Do the Same Drugs Look Different? Pills, Trade Dress, and Public Health}, 365 NEW ENG. J. MED. 83 (2011).

\textsuperscript{160} See infra Figure 3.

\textsuperscript{161} Medicare Part D Drug Spending Dashboard & Data, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.cms.gov/Research-Statistics-
Market share of the two Advair-branded products in Medicare Part D was 82% as compared to market share of 69% in Medicaid. This difference could be explained by increased prescribing of Wixela Inhub and authorized generics in Medicaid. The authorized generic of Advair, manufactured by Prasco, claimed a 10% market share in Medicaid compared to 7% in Medicare Part D. Teva’s authorized generic claimed a 7% market share in Medicaid as compared to only 1% in


162. Supra Figure 3.
163. Id.
Medicare Part D. The ANDA-approved Wixela Inhub has captured 14% share in Medicaid and 10% in Medicare Part D; by contrast, the Teva AirDuo captured less than 1% in both markets, representing just under $1 million (before rebates). These differences between Medicare Part D and Medicaid may be driven by greater cost containment and utilization control policies in Medicaid, such as favorable placement of lower-cost products—including authorized generics—on preferred drug lists or formularies.

Importantly, Medicare Part D spending in 2019 ($2.09 billion before rebates) was over four times as much as 2019 Medicaid spending ($495 million before rebates). The product hop to Advair HFA has also been modestly successful, as it represented 23% of Medicaid spending and 13% of Medicare Part D spending in 2019, with total combined spending (before rebates) of $389.3 million.

5. Impact on Price

The wholesale acquisition cost (WAC) and average wholesale price (AWP) for fluticasone/salmeterol products is shown in Table 2. Other than the AirDuo authorized generic, the AWP is fairly similar across products, implying limited early cost savings to payers from the use of complex generics like Wixela Inhub. From February 2001 to January 2018, the average wholesale price of the Advair Diskus 250/50 increased by over 360%; however, no new price increases were documented since 2018. Since its launch in 2008, the AWP of the Advair HFA 115/21 has increased by over 220%.

164. Id.
165. Id.
167. See Medicare Part D Drug Spending Dashboard & Data, supra note 161; Medicaid Drug Spending Dashboard, supra note 161.
168. Id.
169. IBM MICROMEDEX RED BOOK [hereinafter REDBOOK] (search by Active Ingredient and enter “fluticasone/salmeterol” in the search bar).
170. Id.
171. Id.
Table 2. WAC and AWP for Medium-Strength Fluticasone/Salmeterol Products,\textsuperscript{172}

<table>
<thead>
<tr>
<th>Product Name</th>
<th>WAC</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair Diskus 250/50</td>
<td>$393.93</td>
<td>$472.72</td>
</tr>
<tr>
<td>Advair HFA 115/21</td>
<td>$405.75</td>
<td>$486.90</td>
</tr>
<tr>
<td>AirDuo Digihaler 113/14</td>
<td>$399.00</td>
<td>$478.80</td>
</tr>
<tr>
<td>AirDuo Respilick 113/14</td>
<td>$350.33</td>
<td>$420.40</td>
</tr>
<tr>
<td>Teva Authorized Generic 113/14</td>
<td>$95.40</td>
<td>$119.25</td>
</tr>
<tr>
<td>Prasco Authorized Generic 250/50</td>
<td>$354.15</td>
<td>$444.36</td>
</tr>
<tr>
<td>Wixela Inhub 250/50</td>
<td>$116.44</td>
<td>$449.08</td>
</tr>
</tbody>
</table>

6. Lessons

The Advair experience highlights several lessons for FDA as it evaluates its approach to complex generics for drug-device combinations. First, the rigor of its specifications for replicating the Advair Diskus may have delayed the Mylan and Hikma ANDA approvals by over two years, with other manufacturers facing continued delays. The same issue happened when Teva attempted to replicate Mylan’s EpiPen.\textsuperscript{173} Though the Sandoz Citizen Petition in that case was also denied, it may have hindered Teva’s progress toward a successful ANDA approval.\textsuperscript{174} Precise duplication of the device component may fit the statutory requirements of the ANDA and its labeling, but the added clinical value to patients of an exact replica device may not be substantial.

The fluticasone/salmeterol experience reveals several impediments to robust market competition and lower prices: (1)
tertiary patents obtained by GSK that delayed market entry by several years; (2) challenges in ANDA development by Mylan and others that unintentionally extended the market exclusivity period for Advair Diskus; and (3) limited market penetration and price decreases overall.

B. CASE STUDY 2: ADALIMUMAB [HUMIRA]

Adalimumab is a monoclonal antibody, first approved by the FDA in December 2002 to treat rheumatoid arthritis. Supplemental indications were later approved for a variety of other inflammatory conditions, including “psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, plaque psoriasis, juvenile idiopathic arthritis, ulcerative colitis, pediatric Crohn’s disease, hidradenitis suppurativa, and uveitis.” To date, adalimumab has generated over $170 billion in worldwide net revenue, including $107 billion from United States payers ($16.1 billion in the United States in 2020 alone).

Adalimumab’s key United States patent expired in 2016.

1. Adalimumab Patent Thicket

Over the course of several decades, AbbVie has developed a thicket of patents that has undermined efforts by competing firms to market approved biosimilar products. Unlike the Orange Book, which first listed patents in 1985, the Purple

---


176. Id. (citing Food and Drug Administration, Approved Label for Humira (Mar. 2020) (online at www.accessdata.fda.gov/drugsatfda_docs/label/2020/125057s415lbl.pdf)).

177. Id. at 3.


Book Database of Licensed Biological Products only recently began listing patent information in June 2021, pursuant to the Biological Product Patent Transparency amendments to the BPCIA.\textsuperscript{181} That said, the exact number of patents in AbbVie’s Humira portfolio is not readily knowable.

A 2018 report estimated that AbbVie owns over 110 unexpired patents for adalimumab, including approximately fourteen on its formulation, twenty-four on methods of manufacture, twenty-two on methods of treating particular diseases, and fifteen on other aspects of its technology (including device and diagnostics).\textsuperscript{182} That number may be an underestimate: antitrust litigation proceedings from 2020 and 2021 allege that 130 patents have been issued for Humira out of nearly 250 filed patent applications.\textsuperscript{183} Eighty-nine percent of those patents were filed after adalimumab was approved in 2002, with nearly 50\% of applications filed since 2014.\textsuperscript{184} In the absence of settlements, these patents would delay competition on adalimumab for over four decades since the first patents were filed.\textsuperscript{185}

2. Biosimilars for Adalimumab

Because adalimumab is a biologic, it is not subject to the same regulatory processes as small-molecule drug-device combinations. Instead of deciding whether to pursue a follow-on product via the ANDA or 505(b)(2) pathways, biosimilar

\begin{flushright}


183. Brief and Short Appendix of Plaintiffs-Appellants at 8, UFCW Local 1500 Welfare Fund v. AbbVie Inc., No. 20-02402, (7th Cir. Oct. 5, 2020); see also I-MAK, supra note 179, at 3 (examining the 247 patent applications filed for Humira).

184. I-MAK, supra note 179, at 3 (discussing AbbVie’s patent monopoly on Humira).

185. I-MAK, supra note 179, at 3 (explaining AbbVie’s strategy of delaying competition).
\end{flushright}
manufacturers have a separate pathway for FDA approval.\textsuperscript{186} Biologics are generally produced from living organisms, with complex molecular structures and elaborate synthetic pathways.\textsuperscript{187} This creates technical challenges to their discovery, manufacture, storage, packaging, administration, and use.\textsuperscript{188} As such, the cost to develop biosimilars is estimated to be quite high.\textsuperscript{189} While it may cost $1 to $5 million over a few years to develop a generic version of a small-molecule drug, it may cost hundreds of millions of dollars over as long as ten years to develop a biosimilar.\textsuperscript{190}

Biosimilar manufacturing challenges may be further complicated by the existence of trade secrets, a form of intellectual property protection that protects manufacturing processes or other secret business information.\textsuperscript{191} Unlike patents, trade secret protection does not expire, but it would not prevent competition by businesses that independently develop equivalent processes through work-arounds.\textsuperscript{192} Some have proposed regulatory and legislative remedies to facilitate disclosure of trade secrets by biologics manufacturers.\textsuperscript{193} However, when the FDA approved the first Humira biosimilar in 2016 (adalimumab-atto, Amjevita), it denied AbbVie's Citizen

\begin{thebibliography}{99}
\bibitem{188} \textit{How to Address the Challenges of Biologics Discovery and Development}, LABIOTECH.EU (Nov. 27, 2019), https://www.labiotech.eu/partner/challenges-biologics-development/.
\bibitem{189} \textit{Id.}\textsuperscript{188}
\bibitem{193} See Price & Rai, supra note 191, at 189 (proposing joint FDA and congressional action to spur innovation, such as lengthening regulatory exclusivity periods).
\end{thebibliography}
Petition claiming that trade secrets and other confidential commercial information in the company’s biologics license application (BLA) would be used to benefit biosimilar manufacturers. Seven adalimumab biosimilars have been approved as of December 2021.

3. Patent Challenges and Settlements

Because biologics are larger and structurally more complex than small-molecule drugs, they may be protected by many more patents. The absence of patent information in FDA’s Purple Book has historically made it challenging for potential biosimilar manufacturers to assess the development challenges and litigation risk associated with entering the market. Like generic manufacturers, biosimilar manufacturers must often pursue one of two remaining options: wait for all patents to expire or attempt to overturn the patents in court. For adalimumab and other biologics with highly lucrative markets, biosimilar manufacturers have considerable financial incentive to develop biosimilars despite the high likelihood of patent infringement litigation. There are two primary processes by which biosimilar manufacturers (and other interested parties) can challenge biologic patents.

4. Patent Dance

Under the BPCIA, before an FDA-approved biosimilar is able to enter the United States marketplace, a process known as the “patent dance” often occurs. Although more than one


196. In the dance, the biosimilar company provides its license application to the innovator company, which in turn examines the application for potential patent infringements. Alejandro Menchaca, The Inner Workings of the BPCIA Patent Dance, AM. J. OF MANAGED CARE: THE CTR. FOR BIOSIMILARS (July 24,
patent can be challenged in a single lawsuit, the large numbers of patents in biosimilar disputes substantially increases the complexity, expense, and uncertainty of the proceedings, potentially deterring some biosimilar manufacturers from even attempting to enter the market. In a unanimous decision, the Supreme Court recently ruled that the provision of a biosimilar company's license application to the innovator company is optional and that the 180-day notification period could begin before the biosimilar receives FDA approval.\textsuperscript{197}

After Amgen developed Amjevita and sought to enter the market in 2016, it faced a court challenge over sixty-one adalimumab patents.\textsuperscript{198} A second case from 2017 alleged that Boehringer-Ingelheim’s biosimilar Cyltezo infringed seventy-four adalimumab patents, including several that had been issued in the twelve-month period since the Amgen litigation was initiated.\textsuperscript{199} Importantly, the patent dance limits the number of patents challenged in the first round of litigation, requiring the plaintiff and the defendant in each case to agree to litigate only the ten (Amgen) and eight (Boehringer-Engelheim) most important patents at issue in the cases.\textsuperscript{200} Though this may make the judicial process more efficient and less costly, it does not adequately facilitate challenges to Humira’s vast patent estate. Further, settlements leave these patents intact, so the patent dance has yet to chip away at AbbVie’s patent portfolio.

\textsuperscript{201} https://www.centerforbiosimilars.com/view/the-inner-workings-of-the-bpca-patent-dance. The biosimilar company must also give the innovator company a 180-day notification before marketing its product. \textit{Id.}

\textsuperscript{197} Sandoz, Inc. v. Amgen, Inc., 137 S. Ct. 1664 (2017); see also Ameet Sarpotdar, Abbe R. Gluck & Gregory D. Curfman, \textit{The Supreme Court Ruling in Sandoz v Amgen: A Victory for Follow-on Biologics}, 178 J. AM. MED. ASS’N INTERNAL MED. 5 (2018) (analyzing the potential impact of \textit{Sandoz v. Amgen} and concluding that it may help reduce prices and expand patient access to biosimilars).


5. Inter Partes Review

Recognizing the proliferation of patents and the high costs of patent litigation across all fields of technology, Congress in 2011 created a new administrative procedure for challenging patents: *inter partes* review (IPR). The process takes place before three experienced administrative patent judges of the Patent Trial and Appeal Board (PTAB)—a body within the United States Patent and Trademark Office—and is generally a quicker and cheaper alternative to litigation. However, only a single patent can be challenged per IPR proceeding, making its use in the biologics space potentially cumbersome. Even if some patents are successfully invalidated, any remaining patents could still block biosimilar entry. Despite its limitations, use of IPR has proven extremely popular among patent challengers, with over 1429 challenges in fiscal year 2020, including ninety-eight related to chemical technology and seventy-eight related to biopharmaceutical technology. Multiple biosimilar manufacturers have pursued IPRs of adalimumab patents, but these petitions have led to mixed results. In 2017, the PTAB struck down one such patent in response to a challenge by Coherus BioSciences, but several other IPRs brought by Sandoz, Amgen, and Coherus were unsuccessful.

---

201. Jonathan J. Darrow, Ameet Sarpatwari & Gregory Curfman, *Battling Over Patents: The Impact of Oil States on the Generic Drug Industry*, 19 YALE J. HEALTH POL’Y, L. & ETHICS 250 (2020). Though increasingly used with mixed success, *inter partes* review is also controversial. The industry has lobbied to exempt pharmaceutical and biologic patents from review, and the procedure recently survived a constitutionality challenge before the United States Supreme Court. See Oil States Energy Services, LLC v. Greene’s Energy Group, LLC., 138 S. Ct. 1365 (2018) (upholding the constitutionality of *inter partes* review under Article III and the Seventh Amendment); see also Darrow, Sarpatwari & Curfman, supra (analyzing the aftermath of *Oil States* and the burgeoning role of *inter partes* review in the pharmaceutical sector).


6. AbbVie Product Hops

The initial adalimumab products were packaged as prefilled syringes in various doses. Four years after the initial approval of adalimumab, AbbVie launched the Humira pen; in 2018, it launched a revamped Humira pen in collaboration with Eisai. Though the pens may have the effect of simplifying self-administration by patients, they also have the added benefit of extending the market monopoly of Humira products through the addition of tertiary patents to the product patent portfolio.

In an effort to mitigate the impact of biosimilar entry, AbbVie has also developed new product lines for Humira. In addition to creating starter packs for different indications, AbbVie created a citrate-free formulation of Humira, which it has aggressively advertised since its approval in July 2018. The citrate-free formulation is offered at a higher concentration than regular Humira, and the lack of a citric acid buffer and a higher concentration reportedly lessens pain after use. Promotion of the citrate-free formulation is highly visible at the top of AbbVie’s Humira website. Importantly, Humira

206. Infra Figure 4.
207. Id.
209. In addition to new versions of Humira, AbbVie has also introduced new biologic products risankizumab [Skyrizi] and upadacitinib [Rinvoq] to capture additional market share that may be lost to adalimumab biosimilars. See Walid F. Gellad & Chester B. Good, Adalimumab and the Challenges for Biosimilars, 322 J. AM. MED. ASS’N 2171 (2019).
212. Infra Figure 5.
Citrate-free has new associated patents, which will extend exclusivity beyond 2023.\textsuperscript{213}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Different Formulations of Humira\textsuperscript{214}}
\end{figure}


Prescribe HUMIRA Citrate-free for your new and existing HUMIRA patients

- No citrate buffers\(^1,2\)
- Thinner needle (29 gauge vs 27 gauge)\(^2\)
- 50% less volume (0.4 mL instead of 0.8 mL for HUMIRA 40-mg dose)\(^1\)
- Less pain immediately following injection\(^2\)

*Injection site pain immediately following injection as measured using a 0-10 cm Visual Analog Scale: HUMIRA 40 mg/0.4 mL vs HUMIRA 40 mg/0.8 mL.

Figure 5. Humira Website\(^{215}\)

\(^{215}\) Humira\(^{®}\) (adalimumab) | A Biologic Treatment Option, HUMIRA, http://www.humira.com (last visited Jan. 13, 2022); HUMIRA (adalimumab)
Collectively, the impact will likely be as follows: by the time biosimilar adalimumab products enter the market in 2023, AbbVie will have successfully shifted patients over to other AbbVie products that are not interchangeable with existing biosimilars, thereby preserving substantial market share.  

7. Price Considerations and Market Share

Since 2003, the AWP of Humira has been increased twenty-seven times, reflecting an increase of nearly 550% in nineteen years. According to I-MAK, AbbVie stands to gain an estimated $77 billion from 2018 to 2023 by delaying market entry of biosimilars through settlement agreements. In 2019, adalimumab accounted for $3.72 billion in sales (before rebates) in Medicare Part D and $2.25 billion in sales (before rebates) in Medicaid.

---


218. REDBOOK, supra note 169 (search results by Active Ingredient and enter “adalimumab” in search bar); see also DRUG PRICING INVESTIGATION, supra note 175, at 4.

219. Infra Figure 6.
Figure 6. Market Share of Humira Products as a Percentage of Total Adalimumab Spending, Medicaid and Medicare Part D, 2019.220
Based on 2019 spending, citrate free formulations of Humira have collectively captured 39% of the market share for Medicare Part D and 53% of the market share for Medicaid.²²¹ AbbVie has kept pricing of citrate free formulations on par with its predecessors; AWP unit pricing between regular and citrate-free formulations is equivalent and has been increased by the same percentages annually.²²² In the last few years, AbbVie has begun removing certain Humira formulations from the market, which could constitute hard switches since biosimilars have yet to enter the market.²²³ By delaying biosimilar entry until 2023, AbbVie gave itself a grace period to switch users over from regular to citrate-free formulations of Humira. For those users, biosimilar entry of regular formulations may not result in lower prices. And without automatic substitution or interchangeability, brand loyalists may choose to stick with Humira, especially if patient out-of-pocket costs are comparable. Indication-specific starter packs have separate NDC codes and are reported separately in Medicare Part D and Medicaid dashboards.²²⁴ In Medicare Part D, approximately three-quarters of the starter packs were for citrate free formulations.²²⁵

Given that adalimumab biosimilars have yet to enter the market, there are no realized costs savings due to biosimilars. This is because settlement agreements with nine companies—six of which have approved adalimumab biosimilars—extend to the year 2023, so market competition may change dramatically

²²⁰ Medicare Part D Drug Spending Dashboard & Data, supra note 161; Medicaid Drug Spending Dashboard, supra note 161.
²²¹ See Medicare Part D Drug Spending Dashboard & Data, supra note 161. Each calculation includes spending on citrate-free starter packs.
²²² REDBOOK, supra note 169 (search by active ingredient and enter “adalimumab” in search bar). For instance, all products increased in price by 7.4% in January 2021. Id.
²²³ REDBOOK, supra note 169. According to REDBOOK, four Humira products were deactivated in 2019 and 2020 (identified by national drug classification code, NDC): 00074-3799-06 (deactivated May 8, 2019); 00074-3799-03 (deactivated May 28, 2019); 00074-6347-02 (deactivated Dec. 24, 2019); and 00074-9374-02 (deactivated Mar. 30, 2020). Id.
²²⁴ See Medicare Part D Drug Spending Dashboard & Data, supra note 161.
²²⁵ Id. There were 5109 beneficiaries of citrate free formulations in 2019, compared to 1849 beneficiaries of regular formulations. Id.
at that point. With AbbVie’s considerable market switch to citrate-free formulations, there are questions as to whether the approved adalimumab biosimilars will still be relevant in 2023.

Table 3. AbbVie Settlements with Would-be Humira Challengers and Anticipated Launch Dates.

<table>
<thead>
<tr>
<th>Company/Partner</th>
<th>Drug Name</th>
<th>Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Amjevita*</td>
<td>January 2023</td>
</tr>
<tr>
<td>Samsung Bioepis / Merck</td>
<td>Hadlima*</td>
<td>June 2023</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Cytelzo*</td>
<td>July 2023</td>
</tr>
<tr>
<td>Mylan / Fujifilm Kyowa Kirin Biologics</td>
<td>Hulio*</td>
<td>August 2023</td>
</tr>
<tr>
<td>Sandoz</td>
<td>Hyrimoz*</td>
<td>September 2023</td>
</tr>
<tr>
<td>Fresenius Kabi</td>
<td>MSB11022</td>
<td>September 2023</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Abrilada*</td>
<td>November 2023</td>
</tr>
<tr>
<td>Momenta</td>
<td>M923</td>
<td>December 2023</td>
</tr>
<tr>
<td>Coherus</td>
<td>CH-1420</td>
<td>December 2023</td>
</tr>
</tbody>
</table>

* FDA-approved as of April 2021

8. Lessons

Adalimumab portends a difficult road ahead for manufacturers seeking to create biosimilar-device combinations.

226. *Infra* Table 3.
227. See Brennan, *supra* note 216.
for other top revenue-generating biologics: nearly five years after its key patent expired, Humira faces no direct competition in the United States. Biologics have emerged as essential therapeutic options in the United States, with increasing approvals and expanding utilization over the last several years, but they have also become some of the most expensive therapies.

As compared to small-molecule generics, slower follow-on entry and smaller cost savings from biosimilars have created uncertainty as to whether robust biosimilar competition will ever truly develop.229 Interchangeability designations may emerge as a key requirement for biosimilars to successfully compete with originator biologics. Though most states now allow for interchangeable biosimilar substitution, state policies tend to be more stringent for biologics than for small-molecule drugs.230 On July 28, 2021, the FDA approved the first interchangeable biosimilar, insulin glargine-yfgn [Semglee]; Boehringer Ingelheim’s Humira biosimilar Cyltezo received its interchangeability designation three months later.231

Biosimilar interchangeability requirements, including human factors studies, do not appear to require substantial device similarity, though threshold analyses include physical comparison of device constituent parts and design differences.232 In fact, the FDA notes that “comparative use human factors studies . . . are intended to confirm that the differences in device and labeling between the generic combination product and [the


reference product] are acceptable.” However, given the likelihood of patentable features associated with the brand-name device, listing of tertiary patents in the Purple Book may create similar barriers to market entry for biosimilars as the listing of tertiary patents in the Orange Book has for complex generics. With extensive patent portfolios safeguarding new biologic products, an efficient and cost-effective process for challenging and invalidating improperly issued patents will be essential to the development of a thriving biosimilar marketplace.

C. CASE STUDY 3: NALOXONE [NARCAN AND EVZIO]

1. Injectable Naloxone

Naloxone is a potent opioid receptor antagonist used to reverse respiratory arrest due to opioid-related overdose. It was first approved in April 1971 as an intravenous, intramuscular, or subcutaneous injection and was most commonly used to treat opioid overdose in clinical settings. Generic injectables first entered the market in 1985, but they were not designed for patient use. Studies have demonstrated that generic intravenous medications are most susceptible to

---


234. As noted previously, there does appear to be some pushback against listing tertiary patents in the Orange Book. See Beall & Kesselheim, supra note 79, at 143–44.


shortage, and the early 2021 shortage of naloxone may have been related to disrupted pharmaceutical supply chains during COVID-19. The market for intravenous naloxone has been relatively volatile since its approval, with several naloxone products marketed and subsequently discontinued during that time period, including Par Sterile Products’ version as recently as January 2020.

Given naloxone’s lifesaving properties, efforts were undertaken to develop mechanisms for delivering the drug in non-hospital settings. In response to an increasing need for naloxone for consumer use, kaléo’s Evzio autoinjector was approved in April 2014, an intramuscular injection that delivered a single 0.4 mg dose of naloxone. The device is voice-guided and has detailed instructions printed on the product itself. Two years later, kaléo received approval for a higher dose form of Evzio, 2.0 mg per dose. By 2018, the 0.4 mg/dose product was off the market, leaving only the higher dose. Citing

239. Morgan Godvin, The US Faces a Naloxone Shortage at the Worst Possible Time, FILTER (July 29, 2021), http://filtermag.org/us-naloxone-shortage. Interviewed here, Leo Beletsky speculates that Pfizer, a major manufacturer of the drug, may have been stretched thin due to production volume of COVID-19 vaccines. Id.
240. ORANGE BOOK, supra note 78, at 6-311, 6-312.
241. See generally John Stran et al., Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health Application of an Emergency Medicine, 79 DRUGS 1395, 1395 (2019) (“Over two decades, the concept of ‘take-home naloxone’ has evolved, comprising pre-provision of an emergency supply to laypersons likely to witness an opioid overdose (e.g. peers and family members of people who use opioids as well as nonmedical personnel), with the recommendation to administer the naloxone to the overdose victim as interim care while awaiting an ambulance.”).
“market dynamics and the entrance of alternative products,” kaléo subsequently removed the 2.0 mg/dose Evzio product from the market in September 2020.245

2. Naloxone Spray

At the time Evzio was approved, the intranasal route of administration of naloxone constituted an unapproved use. One such solution involved the combination of a prefilled syringe of naloxone with a mucosal atomization device for intranasal spraying.246 Clinical trials confirmed the efficacy of the intranasal route of administration,247 and the off-label use of intranasal naloxone by nasal atomizer grew in popularity as many programs and communities searched for new solutions to address the overdose crisis.248 However, amid concerns related to the atomizer device, including inconsistent delivery of adequate dose, the manufacturer, Teleflex, voluntarily recalled the product.249

The unexpected recall prompted an urgent need for an alternative mechanism to intranasally deliver naloxone. An intranasal naloxone product [Narcan] was subsequently developed by Adapt Pharma, Inc. and approved by the FDA on November 18, 2015.250

247. See Anne-Marie Kelly et al., Randomised Trial of Intranasal Versus Intramuscular Naloxone in Prehospital Treatment for Suspected Opioid Overdose, 182 MED. J. AUSTL. 24 (2005); Debra Kerr et al., Randomized Controlled Trial Comparing the Effectiveness and Safety of Intranasal and Intramuscular Naloxone for the Treatment of Suspected Heroin Overdose, 104 ADDICTION 2067 (2009).
250. FDA Moves Quickly to Approve Easy-to-Use Nasal Spray to Treat Opioid Overdose, AHDB (Nov. 18, 2015), https://www.ahdbonline.com/in-the-
a researcher who had previously received $3.45 million in federal funding from the National Institute on Drug Abuse from 2010 to 2014 to develop such a product.  

3. Tertiary Patents

Given that the patent covering the small-molecule compound of naloxone has expired, any Orange Book-listed patents for Evzio or Narcan are likely to be tertiary patents covering their delivery devices. Indeed, in 2016, the sole patent covering intranasal naloxone was for “[a]single-use, pre-primed device adapted for nasal delivery of a pharmaceutical composition to a patient by one actuation of said device into one nostril of said patient.” Interestingly, this patent claims the device but lacks drawings or figures of the device. 

There are currently eight patents for Narcan listed in the 2021 Orange Book, all with a common expiration date of March 16, 2035. None of these patents contain drawings or figures of the device.

By contrast, the Evzio device had fifteen listed patents in the 2015 Orange Book, the latest expiring in 2032. All fifteen are device patents with titles such as “Devices, systems and methods for medicament delivery;” “Medicament delivery device configured to produce an audible output;” “Medical injector with compliance tracking and monitoring;” “Medicament delivery device having an electronic circuit system;” and “Medicament delivery device for administration of opioid antagonists including formulations for naloxone.” The latest-issued patent on the list has fifty associated figures. In spite of its market departure, the complexity of the patent portfolio

253. Id.
254. ORANGE BOOK, supra note 78, at ADA 206.
255. U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (35th ed. 2015).
256. Id.
covering the Evzio device will almost certainly deter competitors seeking to produce complex generics. The 2021 Orange Book lists both Evzio products (0.4 mg/ml and 2.0 mg/ml), now with thirty-one patents covering both products, though the product is listed as discontinued in the updated Drugs@FDA website.258 Given that the product has been discontinued, a generic manufacturer has no clear path to replicate the device unless it pursues licensing agreements with kaléo.

The first generic intranasal naloxone spray was approved in April 2019.259 Three months later, in response to a worsening opioid crisis, the FDA announced that it would be prioritizing the review of ANDAs for Narcan and Evzio products to increase access to these essential medications.260

4. Market for Naloxone

A 2016 study of naloxone prescriptions found a split market between branded Narcan nasal spray (36.7%), branded Evzio auto-injector (33.8%), and generic formulations (29.5%).261 In a second study, Evzio was the second most widely-dispensed naloxone product, accounting for 20% of naloxone prescriptions in the United States during the second quarter of 2017.262 Clinical practice guidelines recommend that naloxone be co-

258. The first Evzio device was approved via 505(b)(2). U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., NDA No. 205787 (approved Apr. 3, 2014), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205787Orig1s000Approv.pdf. The second Evzio device was also approved via 505(b)(2). U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH., NDA No. 209862 (approved Oct. 19, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/209862Orig1s000ltr.pdf.


prescribed to high-risk patients taking prescription opioids, but the practice is relatively uncommon.\textsuperscript{263}

In 2019, total spending (before rebates) on Narcan in Medicaid was $45 million; in Medicare Part D, it was $51.3 million.\textsuperscript{264} Medicare Part D spending on nearly 2000 units of Evzio was $9.9 million, corresponding to average spending (before rebates) of over $5,000 per unit; Evzio is not listed in the Medicaid dashboard for 2019, indicating that fewer than fifty units were dispensed nationwide.\textsuperscript{265}

5. Pricing for Naloxone

When launched, 0.4 mg/ml Evzio had an AWP of $862.50 per unit.\textsuperscript{266} By 2015, that price had increased to $1125, followed by a 400\% increase to $5625 per unit, prompting outcry from activists and policymakers alike.\textsuperscript{267} In contrast, the intranasal formulation, Narcan, has been priced at $75 per unit since its launch 2015.\textsuperscript{268} Despite multiple acquisitions and the known link between pharmaceutical product acquisitions and price increases, Narcan’s price has yet to be increased.\textsuperscript{269}

Despite the relatively high cost of a single dose of Narcan, several states have moved toward standing orders for naloxone at pharmacies.\textsuperscript{270} Policymakers have also advocated for

\textsuperscript{263} Rachel E. Barenie et al., \textit{Rates and Costs of Dispensing Naloxone to Patients at High Risk for Opioid Overdose in the United States, 2014–2018}, 43 DRUG SAFETY 669, 669 (2020).

\textsuperscript{264} See Medicare Part D Drug Spending Dashboard & Data, supra note 161; see Medicaid Drug Spending Dashboard, supra note 161.

\textsuperscript{265} See Medicare Part D Drug Spending Dashboard & Data, supra note 161.

\textsuperscript{266} REDBOOK, supra note 169 (search by product name and enter “Evzio” in the search bar).

\textsuperscript{267} REDBOOK, supra note 169 (search by product name and enter “Evzio” in the search bar); see also COMBATTING THE OPIOID CRISIS, supra note 244.

\textsuperscript{268} COMBATTING THE OPIOID CRISIS, supra note 244 (“The WAC for Narcan was $125 with a $75 bulk pricing for government entities.”).


intranasal naloxone to be reclassified from prescription-only to over-the-counter; though it is not clear what effect this will have on price, access would likely improve.\footnote{Corey S. Davis & Derek Carr, Over the Counter Naloxone Needed to Save Lives in the United States, 130 PREVENTIVE MED. 105932 (2020) (“In this Commentary, we argue that FDA can and should immediately reclassify naloxone from prescription-only to over-the-counter status, a change that could save hundreds if not thousands of lives in the United States every year.”).}

6. Higher Doses

As noted above, a higher-dose Evzio product was approved via the 505(b)(2) pathway in 2016 but discontinued by 2020. A new high-dose intranasal formulation (Kloxxado, 8mg/dose) from Hikma Pharmaceuticals was approved via the 505(b)(2) pathway in April 2021.\footnote{FDA Approves Higher Dosage of Naloxone Nasal Spray to Treat Opioid Overdose, U.S. FOOD & DRUG ADMIN. (Apr. 30, 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-higher-dosage-naloxone-nasal-spray-treat-opioid-overdose.} Some have argued that synthetic opioids require higher doses of naloxone to reverse,\footnote{See, e.g., Ronald B. Moss & Dennis J. Carlo, Higher Doses of Naloxone Are Needed in the Synthetic Opioid Era, 14 SUBSTANCE ABUSE TREATMENT, PREVENTION, & POL’Y 6 (2019) (“[W]e propose that higher doses of naloxone are needed to combat the new era of overdoses due to the more potent synthetic opioids such as fentanyl.”).} yet others are skeptical about the need for a higher dose.\footnote{See, e.g., Lucas G. Hill, Claire M. Zagorski & Lindsey J. Loera, Increasingly Powerful Opioid Antagonists Are Not Necessary, 99 INT’L J. DRUG POL’Y 103457, 103457 (2022) (“The proliferation of powerful opioid antagonists could have unintended consequences that are counterproductive to efforts to prevent opioid-related overdose deaths. Precipitated opioid withdrawal is a known risk of naloxone for opioid-tolerant individuals, producing symptoms such as hyperalgesia, diarrhea, and vomiting, particularly at higher doses.”).} With pricing set at the same level as Narcan, Kloxxado is unlikely to significantly increase access to naloxone in the short-term.\footnote{REDBOOK, supra note 169 (search results by product name and enter “Kloxxado” and “Narcan” in the search bar.).}

7. Lessons

Increased access to naloxone is urgently needed to respond to the overdose crisis, which claimed the lives of over 100,000 people in the United States in the twelve-month period ending April 2021.\footnote{Ctrs. for Disease Control & Prevention: National Center for Health Statistics, Drug Overdose Deaths in the U.S. Top 100,000 Annually, CDC (Nov. 2022).} Others have pushed for lowering the cost of

---

\footnote{271. Corey S. Davis & Derek Carr, Over the Counter Naloxone Needed to Save Lives in the United States, 130 PREVENTIVE MED. 105932 (2020) (“In this Commentary, we argue that FDA can and should immediately reclassify naloxone from prescription-only to over-the-counter status, a change that could save hundreds if not thousands of lives in the United States every year.”).}
\footnote{273. See, e.g., Ronald B. Moss & Dennis J. Carlo, Higher Doses of Naloxone Are Needed in the Synthetic Opioid Era, 14 SUBSTANCE ABUSE TREATMENT, PREVENTION, & POL’Y 6 (2019) (“[W]e propose that higher doses of naloxone are needed to combat the new era of overdoses due to the more potent synthetic opioids such as fentanyl.”).}
\footnote{274. See, e.g., Lucas G. Hill, Claire M. Zagorski & Lindsey J. Loera, Increasingly Powerful Opioid Antagonists Are Not Necessary, 99 INT’L J. DRUG POL’Y 103457, 103457 (2022) (“The proliferation of powerful opioid antagonists could have unintended consequences that are counterproductive to efforts to prevent opioid-related overdose deaths. Precipitated opioid withdrawal is a known risk of naloxone for opioid-tolerant individuals, producing symptoms such as hyperalgesia, diarrhea, and vomiting, particularly at higher doses.”).}
\footnote{275. REDBOOK, supra note 169 (search results by product name and enter “Kloxxado” and “Narcan” in the search bar.).}
\footnote{276. Ctrs. for Disease Control & Prevention: National Center for Health Statistics, Drug Overdose Deaths in the U.S. Top 100,000 Annually, CDC (Nov. 2022).}
Narcan through march-in rights, especially given the substantial contribution of federal funding to its development.\(^{277}\) Prior to Evzio’s withdrawal from the market, some called for the federal government to step in and use kaléo’s patents for Evzio under 28 U.S.C. § 1498.\(^{278}\) This might be more feasible now that Evzio is off the market, though intranasal forms have become the preferred method of community naloxone use. The better scenario may be an influx of complex generic competitors to intranasal Narcan, which will substantially lower prices over time. To accomplish this, the FDA must continue to incentivize ANDA applications for Narcan,\(^{279}\) and nonprofit manufacturers should be incentivized to produce intranasal naloxone at cost.\(^{280}\)

Other policy proposals, though they do not relate to combination products, should be noted here. Similar to COVID-19 vaccines, the federal government could make wholesale purchases of naloxone and distribute them to states based on

---


277. Wang & Kesselheim, supra note 237, at 475; 35 U.S.C. § 203 (2021); see also Carolyn L. Treasure, Jerry Avorn & Aaron S. Kesselheim, Do March-In Rights Ensure Access to Medical Products Arising from Federally Funded Research? A Qualitative Study, 93 MILBANK Q. 761, 762 (2015) (“We found that the existence of march-in rights may select for government research licensees more likely to commercialize the results and that they can be used to extract minor concessions from licensees. But as currently specified in the statute, such march-in rights are unlikely to serve as a counterweight to lower the prices of medical products arising from federally funded research.”).

278. See, e.g., Wang & Kesselheim, supra note 237, at 475–77 (“We encourage the government to take corrective action by threatening to use 28 U.S.C. § 1498 to infringe on Kaléo’s patents by importing generics or contracting with another pharmaceutical to produce Evzio. Doing so could pressure Kaléo to produce the drug in exchange for a reasonable royalty.”); Gupta, Shah & Ross, supra note 237, at 2215 (“[The] governments could invoke federal law 28 U.S.C. section 1498 to contract with a manufacturer to act on behalf of the United States and produce less costly versions of Evzio’s patented auto-injector in exchange for reasonable royalties — an approach that was considered for procuring ciprofloxacin during the anthrax threat in 2001.”).

279. Brennan, supra note 260.

need. The federal government could establish a program, akin to the Ryan White HIV/AIDS Program, that funds grants to states, cities, and community-based organizations to provide care and treatment, including procurement and dispensing of naloxone. Had it passed, the Comprehensive Addiction Resources Emergency (CARE) Act of 2019 would have provided over $100 billion in federal funding to state and local governments over a ten-year period; the bill—now seeking $125 billion in federal funding over ten years—was reintroduced with substantial Democratic support on December 16, 2021. Policymakers must also focus on upstream nonpharmaceutical interventions that reduce the number of overdoses, such as fentanyl testing strips, supervised consumption sites, and syringe exchange services.

VII. POLICY RECOMMENDATIONS

The challenges facing competition in the combination product sector are substantial. With lessons from these three case studies in mind, I offer solutions across the life cycle of combination products that, if executed in part or in full, may improve market competition and lower prices.

A. STRENGTHEN INITIAL FDA REVIEW

When combination products are approved, a more thorough and streamlined review process is needed. CDER and CBER arguably do not have the expertise to adequately evaluate drug

---

281. See Gupta, Shah & Ross, supra note 237, at 2215 (“[N]aloxone could be purchased in bulk, which would create stable demand that might motivate additional companies to begin manufacturing the medication — a strategy that’s been used for vaccine manufacturing.”).


284. See Alyssa M. Peckham & Erika H. Young, Opportunities to Offer Harm Reduction to People Who Inject Drugs During Infectious Disease Encounters: Narrative Review, OPEN F. INFECTIOUS DISEASES, 2020 (describing opportunities to reduce harm caused by injecting drugs).
delivery devices, so CDRH and the Office of Combined Products should remain integrally involved in multi-center review of such products. Jointly prepared guidance documents—such as the “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA” from January 2017—are a good start. Pooled expertise for product review is also likely to improve the safety of combination products entering the market, which would mitigate safety-related recalls and mandated device improvements. Postmarket combination product surveillance is also important and will require ongoing input from CDRH officials as well.

In order to disincentivize tertiary patenting and marketing of devices based on unique features, device components for certain classes of combination products could be made more uniform. A standardized respiratory inhaler, for instance, could contribute to increased adherence and improved patient outcomes, not to mention lower costs from more robust competition. Insulin pens are another class of medication delivery devices ripe for standardization. Though this could have a long-term impact on innovation of such devices, that risk may be outweighed by the benefit of substantially lower drug costs in the near-term.

B. PATENT REFORMS TO FACILITATE MARKET ENTRY OF COMPETITORS

Patent reform is also needed. Some have debated whether pharmaceutical patent terms should be shortened. Others argue that the patent dance is unnecessarily onerous. With products like Humira, even the patent dance cannot invalidate enough patents at once, and certainly not when the manufacturer settles every case, leaving those patents in force. IPR proceedings may invalidate some patents, but the USPTO

is similarly limited in the number of patents it can review at a time; its decisions are also subject to judicial review. Finally, the traditional process of patent litigation for small-molecule drugs, and the thirty-month stay it automatically triggers, may provide outsized rewards to brand-name manufacturers for maintaining large patent portfolios.

In fact, patent quantity, not patent quality, appears to have become the key determinant of successful patent litigation. Manufacturers should be discouraged from engaging in product hopping, particularly when the intent is to transfer market share to other branded products before market exclusivity ends. GSK (Advair) and AbbVie (Humira) have each been successful in this regard. There may be progress on this front soon: at President Biden’s direction, the FDA sent a letter to the USPTO, “seeking to facilitate greater awareness of our complementary work and introduce efficiency in our respective workstreams.” The letter also acknowledges the potential misuse of the patent system to “unduly extend market monopolies and keep drug prices high without any meaningful benefits for patients.”

C. COMPLEX GENERIC ANDA OR 505(b)(2)? WHY NOT A NEW APPROACH?

Though imperfect, the small-molecule ANDA pathway created under the Hatch-Waxman Act has been one of the great successes in pharmaceutical policy, substantially lowering drug

288. See generally Dmitry Karshtedt, The More Things Change: Improvement Patents, Drug Modifications, and the FDA, 104 IOWA L. REV. 1129, 1130 (2019) (“This ‘product hopping’ strategy runs counter to the goal of the legislative framework for regulating branded and generic drug approvals, which is to create appropriate incentives for discoveries that elevate the quality of patient care and human health by providing a period of reward for the brand followed by timely and effectual generic entry.”).


291. Id. at 4–5.
prices while fostering the widespread use of safe and effective generic drugs. However, superimposing the complex generic pathway onto the ANDA—with requirements of bioequivalence, label equivalence, and substantial device similarity—has hindered progress in this sector while dissuading would-be competitors looking to market generic combination products.

The FDA guidance notes that ANDA applicants should “seek to minimize differences from the user interface,” though the agency can “accept such design differences if they are adequately analyzed, scientifically justified, and do not preclude approval in an ANDA.” It is also not clear why the FDA insists that “end-users of generic combination products [must be able to] use the generic combination product when it is substituted for the [reference product] without the intervention of the health care provider and/or without additional training prior to use.”

Device re-training can easily be accomplished by health care workers or pharmacists; such re-training could also be required as part of a risk evaluation and mitigation strategies (REMS) program for generic dispensing at the pharmacy level rather than being used as an impediment to complex generic approval.

The device component of generic combination products need not meet the same rigorous equivalence obligations of small-molecule ANDAs to be safe and effective for widespread use. There are aspects of trade dress—such as the size, shape, and color of the Advair Diskus—that need not be replicated for appropriate medical use of a complex generic. Yet the 505(b)(2) process is no panacea either. As an NDA submission, it is more costly for the company to file and more time-consuming for the FDA to review. Moreover, in most cases, 505(b)(2) combination products have failed to gain traction in the market. Retroactively awarding AB Orange Book designations to these products, like the FDA did with Perrigo’s

---

292. Comparative Analysis, supra note 233, at 1–5 (emphasis added). The agency seems to be implying here that even small deviations from the reference device would preclude approval in an ANDA.

293. Comparative Analysis, supra note 233, at 3.

294. REMS have also been invoked to forestall generic competition, though more commonly through refusing to develop a shared REMS, restricting distribution of products or patenting REMS. See Vökinger, Kesselheim, Avorn & Sarpatwari, supra note 8, at 1666–67.

295. See, e.g., Greene & Kesselheim, supra note 159 (exploring the consequences of variations in the appearance of pills).
AndroGel generic, may go a long way toward solving the problem of market penetration, but it fails to address the bureaucratic inefficiency of pursuing approval through the 505(b)(2) pathway.

A new intermediate approval process might be the appropriate solution: it could take the form of a hybrid ANDA/510k approval process. Congress can establish such a process through legislation, making user fees reasonable, requiring CDRH involvement in all approval decisions, and streamlining the process for human factors studies through the development of a more flexible standard of “functional equivalence” for medical device components of combination products. Unlike substantial equivalence, a standard of “functional equivalence” will allow for the development of complex generics with different devices, so long as they perform the same central functions without compromising safety or efficacy. Finally, the FDA should develop a priority list of existing 505(b)(2)-approved products with non-interchangeable designations, encouraging those manufacturers to petition for AB interchangeability.

Manufacturers should also be discouraged from combination product hops, either by substituting a new device (e.g., Advair HFA) or by adjusting formulations or doses of pharmaceuticals within combination products (e.g., Evzio 0.4mg to Evzio 2.0mg). The Federal Trade Commission (FTC) should more closely scrutinize such products for anticompetitive motivations. For instance, given its modest (not to mention unproven) additional clinical value, Humira Citrate-free should not have pre-emptively depleted the potential market share for adalimumab biosimilars so substantially prior to their anticipated market entry in 2023. In addition, altering concentrations or dosing intervals should not generate new market exclusivities for combination products, thereby blocking competitors. Citizen Petitions, which are often filed with


298. Hagen, supra note 210; see also Benjamin N. Rome, Frazer A. Tessema & Aaron S. Kesselheim, U.S. Spending Associated with Transition from Daily
anticompetitive motivations, should also be disregarded by the 
FDA when such documents focus on subtle differences in device 
form or function.

D. CURBING INCENTIVES FOR TERTIARY PATENTING

Once marketed, tertiary patents should not be allowed to 
extend market exclusivity so substantially. As noted above, 
delisting from the FDA’s Orange and Purple Books will help. In 
a recent public comment to the FDA, I made the 
recommendation to delist most secondary patents and all 
tertiary patents from the Orange Book. Transparency is 
important, but when tertiary patents are listed in these 
compendia, onerous standards like Paragraph IV certifications 
prior to launch result in drawn-out processes for patent 
litigation. That said, delisting tertiary patents alone will not 
protect competitors from patent litigation.

Perhaps the best way around this is to allow complex 
generics to develop products using alternative delivery devices. 
The lesson from Mylan’s Wixela Inhub and Teva’s epinephrine 
autoinjector should be that requiring substantial similarity to 
the brand-name device is no simple task. Moreover, the patient 
safety or adherence benefits of substantially equivalent devices 
can be overcome through patient education. Patients can be 
taught to use new medical devices containing the same 
medications as their costlier brand-name equivalents, and 
human factors studies—both pre- and postmarket—can be used 
to evaluate whether patients can safely and effectively 
transition between brand-name and complex generic products.

\[\textit{to 3-Times-Weekly Glatiramer Acetate, 180 J. AM. MED. ASS'N INTERNAL MED.} \]
\[\textit{1165 (2020) (concluding that "[e]xtended market exclusivity from introducing a} \]
\[\textit{new version of an existing brand-name drug can yield manufacturer returns} \]
\[\textit{out of proportion to the level of investment or risk involved; more limited} \]
\[\textit{incentives could encourage incremental innovations to existing drugs at a lower} \]
\[\textit{societal cost"). In this case, it appears to be the formulation, and not the device} \]
\[\textit{patents, standing in the way of generic competition for Copaxone. Copaxone} \]
\[\textit{does not have a "pen" equivalent, though glatiramer acetate is dispensed in} \]
\[\textit{glass syringes, which can be administered using the company's proprietary} \]
\[\textit{autoinjector. See } \textit{Here with Your Dosing Options for Your Lifestyle, COPAXONE,} \]
\[\textit{https://www.copaxone.com/about-copaxone/dosage-information (last visited} \]
\[\textit{Jan. 13, 2022).} \]
\[\textit{299. Michael S. Sinha & Reed F. Beall, Listing of Patent Information in the} \]
\[\textit{Orange Book; Establishment of a Public Docket; Request for Comments;} \]
\[\textit{Reopening of Comment Period, REGULATIONS.GOV (Apr. 15, 2021),} \]
\[\textit{https://www.regulations.gov/comment/FDA-2020-N-1127-0028.} \]
Brand-name manufacturers should also be disincentivized from making any patent-protected manufacturing changes to brand-name drug-device and biologic-device combinations when such changes do not meaningfully add clinical benefit. This may have factored into AbbVie’s decision to switch Humira from pre-filled syringes to single-use pens.300

E. FIXING BIOSIMILARS AND BIOLOGIC DRUG-DEVICES

Biosimilar-device products—and more generally, biosimilars—need a quicker path to market, which requires greater clarity from the FDA regarding the studies needed to demonstrate interchangeability. This may require statutory change, as the BPCIA requires that interchangeable biosimilars “be expected to produce the same clinical result as the reference product in any given patient.”301 Given the complexity of biologics and the role of trade secrets in limiting exact replication,302 some leniency may be justifiable. Principles of noninferiority, often discussed in the context of antibiotics, may be particularly applicable when comparing biologics to biosimilars.303 Once biologics obtain interchangeability designations, state biosimilar product selection laws should be amended to facilitate switching; though most states already require the interchangeability designation as a condition of switching from biologics to biosimilars, many still require physician consent before a switch can be made.

More work should be done to address misconceptions and skepticism of biosimilars.304 Physicians continue to express reluctance toward switching patients from biologics to biosimilars regardless of clinical equivalence and cost

300. See HUMIRA, supra Figure 4. Of note, the FDA does have guidance for manufacturers seeking to transition to new delivery devices. See U.S. FOOD & DRUG ADMIN., BRIDGING FOR DRUG-DEVICE AND BIOLOGIC-DEVICE COMBINATION PRODUCTS: GUIDANCE FOR INDUSTRY 1 (2019).


302. See generally Price & Rai, supra note 191 (exploring the consequences of trade secrecy on biosimilar development).


savings. And fewer than half of physicians in a 2016 survey noted they would be comfortable prescribing biosimilars when they become available; about 40% indicated they would need more education on biosimilars prior to prescribing. Alternative delivery devices may add to this skepticism, but biosimilar REMS programs that require patient training prior to dispensing may alleviate those concerns.

Finally, the biologic-biosimilar settlement problem must be solved. As in the case of AbbVie and Humira, when such settlements are nothing more than market-sharing agreements in disguise, they may run afoul of antitrust laws. Increased FTC scrutiny of settlement agreements should curb some of the more egregious practices.

VIII. CONCLUSION

The advent of increasingly complex combination products has significantly changed the paradigm for how generic competitors can and should enter the market once exclusivity ends. The FDA continues to face challenges with its approach to complex generics, such that ANDA applicants receive multiple CRLs and many manufacturers opt to pursue the 505(b)(2) pathway as a clearer path to market entry. A new, intermediate pathway for complex generics would acknowledge that the ANDA pathway is ill-suited for such products, yet the NDA is costly, inefficient, and does not lead to robust market competition. An intercenter review process, involving FDA officials in CDER, CBER, CDRH, and the Office of Combination Products, may be needed to remedy both the initial approval process for innovators and the subsequent approval process for complex generics and biosimilar-device products.

Ultimately, progress toward meaningful price competition among combination products will need to come through

305. See Richard G. Frank, Friction in the Path to Use of Biosimilar Drugs, 378 NEW ENG. J. MED. 791, 791 (2018) (“[M]ultiple surveys of physicians reveal that even those who routinely use biologic products do not have a clear understanding of biosimilar products. Physicians are therefore naturally hesitant to prescribe biosimilars — especially given that regulations create the impression that a biosimilar may not be all that similar to its originator.” (citation omitted)).


interchangeability and automatic substitution at the level of dispensing. Just as brand-brand competition in the small-molecule drug space has not led to significant cost reductions, 505(b)(2)-approved brand-name “generics” are unlikely to significantly lower the cost of flagship drug-device combinations or meaningfully cut into their market share and revenue streams. The extent to which price competition develops in this sector will depend on the FDA’s ability to resolve regulatory uncertainty around the complex generic approval process.