Generic Substitution Laws and Combination Products

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ABSTRACT

Generic substitution laws have greatly expanded the market share of generic drugs by allowing seamless substitution of cheaper generic drugs for more expensive pioneer drugs. These are state laws that provide a legal mechanism for a pharmacist to dispense a substitute drug deemed equivalent to the prescribed drug. However, with the proliferation of combination products, significant flaws in these laws have become apparent in recent years. Particularly, their more traditional approach to equivalency determination is inadequate in allowing appropriate substitution for a subset of combination products. A multi-pronged approach at the federal, state, and prescriber level is needed to address these limitations.

I. INTRODUCTION

Generic substitution laws have been effective in facilitating the substitution of cheaper, usually generic drugs in place of the more expensive pioneer (brand name) drugs.[1] However, these laws have significant shortcomings in dealing with a portion of the combination product market. Combination products relevant to our discussion are U.S. Food and Drug Administration (FDA)-regulated products comprising two or more different regulated components (i.e., some combination of drugs, biologics, and devices).[2] This Article focuses on a limited subset of these combination products, which FDA classifies as Type 2 (prefilled drug delivery devices/systems) or Type 3 (prefilled biologic delivery devices/systems).[3] Our discussion is further narrowed to apply to only such products that are intended to be prescribed to patients for use in an outpatient setting, without the direct supervision or involvement of a healthcare provider, and usually dispensed by a pharmacist. Examples include, but are not limited to, prefilled drug (or biologic) syringes, auto-injectors, metered-dose inhalers, dry powder inhalers, and nasal sprays. Hereinafter, any mention of the term "combination

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1 CONG. BUDGET OFF., HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY ix (1998), https://www.cbo.gov/sites/default/files/105th-congress-1997-1998/reports/pharm.pdf.

2 *See* 21 C.F.R. § 3.2(e).

3 *Combination Product Definition Combination Product Types*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types (last updated Feb. 15, 2018).

product" denotes only the above-described subset of combination products. As it will be illustrated later, generic substitution laws are only implicated when dispensing pharmaceuticals to patients at a pharmacy and are generally not relevant to other types of combination products; therefore, these other types are excluded from this Article.

The obstacle associated with generic substitution laws and combination products arises from the limitations placed on substitution under state law. These limitations may have been suitable for oral small molecule drugs but create unnecessary barriers for combination products. Considering the anticipated exponential growth in combination products in the coming years,[4] addressing this shortcoming is more critical than ever.

In this Article, I will first briefly review the history of generic drugs, biosimilars, and interchangeable biosimilars. Then I will examine state-level substitution laws and the interplay between them and FDA. This is followed by evaluating the structural failures of substitution laws in relation to combination products. Finally, I will explore potential solutions.

II. GENERIC DRUGS AND BIOSIMILARS

A. Generic Drugs

To facilitate generic drug development and manufacturing, Congress passed the Drug Price Competition and Patent Term Restoration Act (aka the Hatch–Waxman Act) in 1984.[5] The Hatch–Waxman Act allows applicants to use an abbreviated application process (Abbreviated New Drug Application [ANDA]) to obtain FDA approval for marketing generic drugs. Essentially, the ANDA pathway only requires demonstrating therapeutic equivalence between the generic and the pioneer drug, also known as the Reference Listed Drug (RLD).[6] The generic drug applicant relies on the pioneer drug's safety and efficacy studies,[7] thus bypassing costly studies and processes associated with the approval of a new drug usually required under a New Drug Application (NDA).[8] The Hatch–Waxman Act also addressed issues related to pioneer drug exclusivity, generic drug exclusivity, patent term, and patent adjudication, which are beyond the scope of our discussion.[9] In summary, the generic drug can be

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[4] *Drug Device Combination Products Market Size, Share & Trends Analysis Report By Product (Transdermal Patches, Inhalers, Infusion Pumps, Drug Eluting Stents, Antimicrobial Catheters), And Segment Forecasts, 2022 – 2030*, GRAND VIEW RES., https://www.grandviewresearch.com/industry-analysis/drug-device-combination-market (last visited May 17, 2023); *With FDA Combination Products on the Rise, A Common Question is, "Which Regulatory Path Should I Choose?"*, PHARM. DEV. GRP., https://pharmdevgroup.com/fda-combination-products-on-the-rise-which-regulatory-path-should-i-choose/ (last visited Apr. 4, 2023).

[5] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

[6] U.S. FOOD & DRUG ADMIN., EVALUATION OF THERAPEUTIC EQUIVALENCE: DRAFT GUIDANCE FOR INDUSTRY (July 2022), https://www.fda.gov/media/160054/download.

[7] Michael A. Carrier, Mark A. Lemley & Shawn Miller, *Playing Both Sides? Branded Sales, Generic Drugs, and Antitrust Policy*, 71 HASTINGS L.J. 307, 312 (2020).

[8] *Abbreviated New Drug Application (ANDA)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda (last updated Dec. 16, 2022) [hereinafter *FDA ANDA*].

[9] *See* Carrier, Lemley & Miller, *supra* note 7, at 312–13.

introduced into the market under an approved ANDA, after any applicable pioneer drug patent protections and exclusivity period(s) are no longer applicable.[10]

Before the Hatch–Waxman Act, only 35% of top-selling drugs that were no longer under patent protection had generic equivalents; by the late 1990s, almost all such drugs had generic equivalents.[11] However, from a cost perspective, more notable is the exponential growth in the generic drug market share; now, generic drugs constitute over 85% of U.S. prescriptions, resulting in a significant reduction in pharmaceutical spending.[12] Studies have estimated that the proliferation of generics resulted in nearly $2.2 trillion in savings between 2010 and 2020.[13] These cost savings have been realized by payers and patients.[14] Studies have also demonstrated a direct correlation between decreasing out-of-pocket medication costs for patients and improving medication adherence.[15] Moreover, medication nonadherence, especially in chronic illnesses, can lead to an increase in preventable morbidity, mortality, and healthcare costs.[16] Therefore, increasing the market penetration of cheaper pharmaceuticals will decrease direct pharmaceutical spending. It will also decrease the overall healthcare spending by reducing morbidity and mortality associated with medication nonadherence.

The Hatch–Waxman Act facilitated the introduction of generics into the market by providing various incentives to generic drug producers. However, other factors also contributed to the growth in the market share of generic drugs.[17] One of the main drivers for this growth has been state-level generic substitution laws and the promotion of such laws by various payers.[18] Generic substitution laws are discussed in detail later. Still, briefly, these are state laws that permit or require pharmacists to dispense cheaper, usually generic alternatives of the prescribed drug in lieu of the more expensive, usually pioneer drug, even if the prescription is written for the pioneer

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[10] *Expanding the Use of Generic Drugs*, OFF. OF THE ASSISTANT SEC'Y FOR PLAN. & EVALUATION, https://aspe.hhs.gov/reports/expanding-use-generic-drugs-0 (last updated Dec. 1, 2010).

[11] CONG. BUDGET OFF., *supra* note 1, at xii.

[12] Ravi Gupta, Aaron S. Kesselheim, Nicholas Downing, Jeremy Greene & Joseph S. Ross, *Generic Drug Approvals Since the 1984 Hatch–Waxman Act*, 176 JAMA INTERNAL MED. 1391, 1391 (2016).

[13] 2020 GENERIC DRUG & BIOSIMILARS ACCESS & SAVINGS IN THE U.S. REPORT, ASS'N FOR ACCESSIBLE MEDS. 1, 18 (2020), https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pdf.

[14] Ahmed Ullah Mishuk, Ifedolapo Fasina & Jingjing Qian, *Impact of U.S. Federal and State Generic Drug Policies on Drug Use, Spending, and Patient Outcomes: A Systematic Review*. 16 RSCH. SOC. ADMIN. PHARM. 736, 743 (2019).

[15] Michael E. Chernew, Mayur R. Shah, Arnold Wegh, Stephen N. Rosenberg, Iver A. Juster, Allison B. Rosen, Michael C. Sokol, Kristina Yu-Isenberg & A. Mark Fendrick, *Impact of Decreasing Copayments on Medication Adherence Within a Disease Management Environment*, 27 HEALTH AFFS. 103, 107–10 (2008).

[16] Michael E. Chernew, Iver A. Juster, Mayur Shah, Arnold Wegh, Stephen Rosenberg, Allison B. Rosen, Michael C. Sokol, Kristina Yu-Isenberg & A. Mark Fendrick, *Evidence That Value-Based Insurance Can Be Effective*, 29 HEALTH AFFS. 530, 530–31 (2010); Chelsea K. Sanchez, Nicole Farrell & Elisabeth Lapp, *Generic Drugs, Cost, and Medication Adherence*, 40 U.S. PHARMACIST 14, 14–19 (2015).

[17] *See* CONG. BUDGET OFF., *supra* note 1.

[18] *Id.*

drug.[19] In the absence of legal authorization through state-level generic substitution laws, the pharmacist has no legal mechanism to dispense a medication other than the one stated on the prescription.[20]

B. Biologics, Biosimilars, and Interchangeable Biosimilars

Distinct from small-molecule drugs that are synthesized using traditional laboratory techniques, biopharmaceuticals (also referred to as biologics) are "isolated from a variety of natural sources" (e.g., human, animal, or microorganism).[21] It has been said that biologics "come from a living organism" rather than "a set recipe."[22] In contrast to small-molecule drugs, where the manufacturing process is ordered and resistant to change, with biologics, "the product is the process" and, therefore, sensitive to changes.[23] Consequently, unlike small-molecule pioneer drugs that can have their chemical structure exactly replicated in their generic forms, biologics are sensitive to a given manufacturing process, and such replication is not possible.[24] Generics of small-molecule drugs can undergo an abbreviated approval process as described above, but no such abbreviated pathway existed under federal law for biologic products until more recently.[25] This pathway was created under the Biologics Price Competition and Innovation Act (BPCIA) of 2009 as part of the Patient Protection and Affordable Care Act (PPACA).[26] Biologic products that use this abbreviated pathway as a "follow-on biologic" are referred to as biosimilars rather than a *generic* since, in the context of small-molecule drugs, the term *generic* implies identical.[27] The BPCIA provided a twelve-year exclusivity period for the reference biologic product but also delineated the abbreviated pathway for biosimilars.[28] The BPCIA created two categories for biosimilars to enter the market, either as a biosimilar or as an interchangeable biosimilar, each with different regulatory requirements and implications.[29]

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[19] Jeffrey J. Masters, *Not Exactly the Same: An Examination of How Generic Substitution Laws Inadequately Protect Consumers' Needs If Taking Generic Drugs Results in Injuries*, 8 DREXEL L. REV. 233, 240 (2015).

[20] William H. Shrank, Niteesh K. Choudhry, Jessica Agnew-Blais, Alex D. Federman, Joshua N. Liberman, Jun Liu, Aaron S. Kesselheim, M. Alan Brookhart & Michael A. Fischer, *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid,* 29 HEALTH AFFS. 1383, 1383–84 (2010).

[21] *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers (last updated Feb. 6, 2018).

[22] Lindsay Kelly, *Biologics in the Practice of Law*, 39 HARV. J.L. & PUB. POL'Y 21, 21 (2016).

[23] Kasey E. Koballa, *The Biologics Price Competition and Innovation Act: Is a Generic Market for Biologics Attainable*, 9 WM. & MARY BUS. L. REV. 479, 482 (2018).

[24] Favour Danladi Makurvet, *Biologics vs. Small Molecules: Drug Costs and Patient Access*, 9 MED. DRUG DISCOVERY 1, 1 (2021).

[25] Gary M. Fox, *Suggestions for State Laws on Biosimilar Substitution*, 24 MICH. TELECOMM. & TECH. L. REV. 253, 260 (2018).

[26] *See* Koballa, *supra* note 23, at 483.

[27] CONG. RSCH. SERV., FDA REGULATION OF FOLLOW-ON BIOLOGICS 1, 1 (2010), https://crsreports.congress.gov/product/pdf/RL/RL34045/19.

[28] *See* Koballa, *supra* note 23, at 483; *see also* 42 U.S.C. § 262(k)(7).

[29] Koballa, *supra* note 23, at 486.

Biosimilars are biologic products that are highly similar to and have no clinically meaningful differences in safety, purity, or potency (i.e., safety and effectiveness) from the reference product.[30] This contrasts with the regulatory scheme for generics, where the generic must essentially be identical (not just "highly similar") to the pioneer drug.[31] The biosimilarity must be established based on animal, clinical, and/or analytic studies.[32] Among other requirements, the applicant must demonstrate that the biosimilar utilizes the same mechanism for condition(s) of use in the proposed labeling and that those condition(s) of use have been approved for the reference product.[33] The route of administration, dosage form, and strength must also be the same as the reference product.[34]

Interchangeable biosimilars (sometimes referred to as simply interchangeables) are biologic products that are biosimilar and have met additional requirements outlined by the BPCIA.[35] In particular, interchangeables are expected to produce the same clinical results as the reference product.[36] For products that are administered more than once, the risk in terms of safety and reduced efficacy if alternating or switching between the interchangeable and the reference product is not greater than the risk of using the reference product without such alternation or switching.[37] Furthermore, interchangeable designation indicates that FDA has determined that the product can be substituted for the reference product without the intervention of the prescriber.[38]

The term "reference product" for biologics is analogous to RLD for small-molecule drugs. It denotes a single biologic product licensed by FDA under section 351(a) of the Public Health Service (PHS) Act.[39] A reference product can be used to evaluate an application for another biologic product submitted under section 351(k).[40] Section 351(k) delineates the abbreviated pathway for biosimilars and interchangeable biosimilars (analogous to ANDA pathway for drugs). An application for a reference product is often referred to as a "standalone" application as it does not depend on any other biologic product and is submitted with complete safety and effectiveness information (analogous to an NDA).[41] On the other hand, biosimilars and

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[30] 42 U.S.C. § 262(i)(2).

[31] Celia Lu & Elsen C. Jacob, *Biosimilars: Not Simply Generics*, 44 U.S. PHARMACIST 36, 36–39 (2019).

[32] U.S. FOOD & DRUG ADMIN., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY 4 (Apr. 2015), https://www.fda.gov/media/82647/download [hereinafter FDA, DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT].

[33] 42 U.S.C. § 262(k)(2).

[34] *Id.*

[35] *Biosimilar and Interchangeable Biologics: More Treatment Choices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices (last updated Oct. 12, 2021); 42 U.S.C. § 262(k)(4).

[36] 42 U.S.C. § 262(k)(4).

[37] *Id.*

[38] *See* 42 U.S.C. § 262(i).

[39] *Id.*

[40] *Id.*

[41] *Review and Approval*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval (last updated Dec. 13, 2022).

interchangeable biosimilars rely in part on the safety and effectiveness information provided as part of the application for the approval of the reference product.[42]

III. HISTORY OF GENERIC SUBSTITUTION LAWS

To better appreciate the deficiencies of generic substitution laws concerning combination products, it may be helpful to first examine how states regulate the substitution for small-molecule drugs and biologic products.

A. Small-Molecule Drugs

After World War II, there was a significant rise in the development of new and potent drug entities and an increase in prefabricated drug products, decreasing the amount of compounding by pharmacies.[43] Consequently, enormous growth in pharmaceutical sales was observed, particularly among manufacturers of proprietary drug products. This was followed by organized efforts by pharmaceutical companies to prohibit prescription drug substitution.[44] These organized efforts, coupled with concerns regarding counterfeiting, resulted in every jurisdiction, except for the District of Columbia, passing laws, dubbed anti-substitution laws, prohibiting the substitution of drugs and mandating pharmacists to fill prescriptions exactly as written.[45]

However, starting in the 1970s, states concerned with the rise of the cost of prescription drugs for public and private payers—while encouraged by the federal efforts to facilitate the marketing of generic drugs—repealed their anti-substitution laws.[46] This was followed by all states amending their laws to allow for the substitution of cheaper, typically generic drugs, for more expensive, typically pioneer drugs.[47] These laws have increased generic use and reduced patient and payer spending on prescriptions without negatively impacting patients' health-related quality of life.[48] By the mid-1980s, all states had repealed their anti-substitution laws and adopted generic substitution laws instead.[49] The nuances of the generic substitution laws differ from state to state—some state laws mandate substitution by the pharmacist, while others permit such substitution at the discretion of the pharmacist; some state laws require explicit patient consent, while others assume implicit consent for such substitutions; some use positive formularies (i.e., limiting drug substitution to a specific list), while others use a negative formulary (i.e., allow substitution unless prohibited by a specific list).[50] Furthermore, some states require substitution to be based on the Orange Book (details discussed later), while others allow for a more expansive authority beyond the

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42 *See* Lu & Jacob, *supra* note 31.

43 TONY BURTON, THEODORE GOLDBERG & CAROLEE DEVITO, GENERIC DRUG LAWS: A DECADE OF TRIAL—A PRESCRIPTION FOR PROGRESS 125–26 (Theodore Goldberg ed., 1986).

44 *Id.*

45 *Id.*

46 *Id.*

47 Yan Song & Douglas Barthold, *The Effects of State-Level Pharmacist Regulations on Generic Substitution of Prescription Drugs*, 27 HEALTH ECON. 1717, 1717–18 (2018).

48 *See* Mishuk, Fasina & Qian, *supra* note 14, at 738–39.

49 *See* Song & Barthold, *supra* note 47, at 1719.

50 Jesse C. Vivian, *Generic-Substitution Laws*, 33 U.S. PHARMACIST 30, 30–34 (2008).

Orange Book.[51] Common among these laws is the elimination of the need to obtain affirmative authorization from the prescriber for allowed substitutions within the parameters of the respective state law.[52] Moreover, all states allow the prescriber to restrict substitution, although some require justification for such restriction.[53] All states also allow the patient to decline the substitution if so inclined.[54] Although substitution may be prohibited by the prescriber or refused by the patient, payers must make an independent judgment regarding coverage for a potentially more expensive pioneer drug.[55] Regardless of how each state approached the issue of drug substitution, the underlying principle was to provide a mechanism for pharmacists to dispense cheaper substitute drugs that contain the same active ingredient without needing an affirmative authorization from the prescriber.

B. Biologics

The above-described regulatory scheme has been in place for small-molecule drugs for decades with remarkable success. However, the introduction of biologic, biosimilar, and interchangeable biosimilar products in the 21st Century required updating the regulatory scheme for substitution laws. As a result of the differences between small-molecule drugs and biologic products previously discussed, states had to create novel regulatory pathways to address the shortcomings of the generic substitution laws developed in a bygone era. In the past decade, all fifty states, the District of Columbia, and Puerto Rico have amended their respective substitution laws to allow for the substitution of biological products, although that delegation of authority has generally been limited to interchangeable biosimilars.[56]

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[51] *Id.*

[52] *Id.*; *See, e.g.*, Haw. Rev. Stat. § 328-92; Nathan D. Pope, *Generic Substitution of Narrow Therapeutic Index Drugs*, 34 U.S. PHARMACIST 12, 12–19 (2009);

[53] New York ex rel. Scheiderman v. Actavis PLC, 787 F.3d 638, 645 (2d Cir. 2015) (stating that every state either "permit[s] or require[s] pharmacists to dispense a therapeutically equivalent, lower-cost generic drug in place of a brand drug absent express direction from the prescribing physician that the prescription must be dispensed as written"); Erika Lietzan, *Ignoring Drug Trademarks*, 56 WAKE FOREST L. REV. 945, 948 (2021); *See* Fox, *supra* note 25, at 257 (also noting, "In response, some states have begun requiring physicians to write down why prescriptions must be filled with brand-name drugs. After passing such a law, Massachusetts saw a 'dramatic' decrease of $150 million in its Medicaid spending.").

[54] *See* Vivian, *supra* note 50.

[55] *See, e.g.*, *DAW Codes: What Pharmacies Need to Know*, RX INSIDER (Dec. 14, 2022), https://rxinsider.com/market-buzz/?p=13709-daw-codes-what-pharmacies-need-to-know; WASH. ST. HEALTH CARE AUTH., PRESCRIPTION DRUG PROGRAM BILLING GUIDE 114 (Jan. 19, 2018), https://www.hca.wa.gov/assets/billers-and-providers/prescription-drug-bi-20180119.pdf.

[56] *See, e.g.*, CARDINAL HEALTH, BIOSIMILAR INTERCHANGEABILITY LAWS BY STATE (2021), https://www.cardinalhealth.com/content/dam/corp/web/documents/publication/Cardinal-Health-Biosimilar-Interchangeability-Laws-by-State.pdf (last visited May 18, 2023). NAT'L ASS'N OF CHAIN DRUG STORES, STATE SUBSTITUTION PRACTICES FOR BIOLOGICAL DRUGS (July 2021), https://www.nacds.org/pdfs/government/2021/State-Substitution-Practices-for-Biological-Drugs-chart-July-2021.pdf (last visited May 1, 2023); *Oklahoma Becomes Final State to Permit Biosimilar Substitution*, SAFE BIOLOGICS (Apr. 2021), https://safebiologics.org/2021/05/oklahoma-becomes-final-state-to-permit-biosimilar-substitution/ (last visited May 1, 2023).

IV. ORANGE BOOK

In the late 1970s, due to several requests from various states regarding therapeutic equivalence determination and development of formularies to facilitate generic substitution, FDA developed the *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) and, more recently, the online version, the Electronic Orange Book.[57] Among other products, and as required by law, the Orange Book lists approved prescription drug products, their therapeutic equivalents (if any), and any applicable patent and exclusivity information for these drugs.[58] FDA clearly differentiates between the Orange Book's therapeutic equivalence determination, an objective and scientific judgment, and generic substitution, which may involve social and economic policy administered by the states.[59] Furthermore, FDA does not consider the content of the Orange Book to be an official FDA action or legally binding.[60] Despite this, many states have incorporated the Orange Book's therapeutic equivalence determination into their generic substitution laws and regulations, thus elevating its status to a legally binding source.[61]

The Orange Book lists all RLDs.[62] An RLD is a new drug product that has been approved under the Federal Food, Drug, and Cosmetic Act (FDCA) and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[63] An RLD is identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.[64] By definition, an approved ANDA is based on establishing therapeutic equivalence between the generic drug and the RLD—and will be listed as such in the Orange Book.[65]

To better appreciate the significance of FDA's definition of therapeutic equivalence as a criterion for inclusion in the Orange Book, it is necessary to examine its legal definition. *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated. They can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[66] *Pharmaceutical equivalents* are drug products with identical dosage forms and route(s) of administration containing equal amounts of the same active drug ingredient.[67] *Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents becomes available at the site of drug

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[57] *Orange Book Preface*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface (last updated on Jan 24, 2023).

[58] *Id.*

[59] *Id.*

[60] *See* Vivian, *supra* note 50.

[61] *Id.*

[62] AMIRALA S. PASHA, LAWS OF MEDICINE: CORE LEGAL ASPECTS FOR THE HEALTHCARE PROFESSIONAL 363 (Amirala S. Pasha ed., 1st ed. 2022).

[63] *See Orange Book Preface*, *supra* note 57.

[64] 21 C.F.R. §314.3(b).

[65] *See FDA ANDA*, *supra* note 8.

[66] 21 C.F.R. § 314.3(b).

[67] *Id.*

action when administered at the same molar dose under similar conditions.[68] From FDA's perspective, products found to be therapeutically equivalent can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling, but it does not indicate that the products are identical.[69] For instance, two therapeutically equivalent products may have different shapes, flavors, and coloring.[70]

The Orange Book uses a coding system composed of two letters. The code denotes if a drug product is therapeutically equivalent to other pharmaceutically equivalent products (first letter) and additional information based on FDA's evaluation for such determination (second letter).[71] In the Orange Book's coding scheme, an initial letter "A" designates drug products that FDA considers to be therapeutically equivalent to other approved pharmaceutically equivalent products. In contrast, an initial letter "B" designates drug products that FDA considers not to be therapeutically equivalent to any other approved pharmaceutically equivalent products.[72] For instance, Prozac, the RLD, and its therapeutically equivalent drug (generic version), fluoxetine, are coded as "AB," where the initial letter "A" in the code indicates therapeutic equivalence.[73] Meanwhile, Adrenaclick, an epinephrine autoinjector, is coded as "BX" where the initial letter "B" indicates that FDA does not consider the product to be therapeutically equivalent to any other currently approved pharmaceutically equivalent product.[74]

V. PURPLE BOOK

The *List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* (aka Purple Book) serves a similar purpose as the Orange Book, but for biologics instead of small-molecule drugs.[75] Since February 2020, a single list of all FDA-approved biological products has been available in the Purple Book database.[76] Before that date, the Purple Book was available as two separate lists, one for FDA-licensed biologic products regulated by the Center for Drug Evaluation and Research (CDER) and one for FDA-licensed biologic products regulated by the Center for Biologics Evaluation and Research

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[68] *Id.*

[69] *See Orange Book Preface*, *supra* note 57.

[70] *Id.*

[71] *Id.*

[72] *Id.*

[73] *Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (search for "Prozac" under "Search by Proprietary Name, Active Ingredient or Application Number") (last visited Apr. 17, 2023).

[74] *Id.* (search for "Adrenaclick" under "Search by Proprietary Name, Active Ingredient or Application Number") (last visited Apr. 21, 2023); *see also Orange Book Preface*, *supra* note 57 ("Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.").

[75] *Background Information: List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/background-information-list-licensed-biological-products-reference-product-exclusivity-and (last updated Aug. 3, 2020).

[76] *Id.*

(CBER).[77] In addition to listing the reference biologic product, the Purple Book lists their biosimilar and interchangeable products, if any.[78] This is similar in concept to how generic drugs and their RLDs are listed in the Orange Book. However, due to the inherent nature of biologics, significant differences exist between the regulatory treatment of generic drugs and biosimilar and interchangeable products.[79]

VI. COMBINATION PRODUCTS

Combination products were formally recognized through the enactment of the Safe Medical Devices Act of 1990, which added section 503(g) to the FDCA.[80] Combination products are typically reviewed under a single application to facilitate the agency's review. The primary jurisdiction for review is assigned to the relevant FDA center based on the product's primary mode of action.[81] The Act defines the primary mode of action as "the single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product."[82] Therefore, with some exceptions if the primary mode of action is a drug, the combination product is assigned to the Center for Drug Evaluation and Research (CDER); if a biologic, to the Center for Biologics Evaluation and Research (CBER); and, if a device, to the Center for Devices and Radiological Health (CDRH).[83]

Combination products create a unique challenge to substitution laws. Not only must the drug (or the biologic) component meet the regulatory criteria, but the device portion must be sufficiently similar for the combination product to be approved under the applicable abbreviated pathways.[84] Stated differently, the similarity of the device portion of the proposed combination product to the device portion of the reference combination product is considered when determining eligibility for approval under an ANDA for a drug–device combination product or under the 351(k) pathway for a

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[77] *Id.*

[78] *Id.*

[79] *See, e.g.*, Lu & Jacob, *supra* note 31 ("The BPCIA permits the FDA, following a period of market exclusivity for reference products, to approve biological products if they have the same primary amino acid sequence and mechanism of action as the reference product and there are no clinically meaningful differences between the reference product and the biosimilar. Because each reference product's manufacturing process is proprietary information, the manufacturer's biosimilar product always differs slightly from the reference product. This is in contrast to generic medications, which are identical to brand medications. Therefore, although there are some similarities between generic and biosimilar medications, biosimilars are not considered generic versions of biological products.").

[80] Suzanne O'Shea, *Working Through the US Rules for Combination Products*, REGUL. AFFS. J. PHARMA, 651 (Oct. 2008), https://www.faegredrinker.com/webfiles/Working%20Through%20the%20U.S.%20Rules%20for%20Combination%20Products.pdf.

[81] *Frequently Asked Questions About Combination Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products (last updated Aug. 16, 2022) [hereinafter *Combination Products FAQs*].

[82] 21 U.S.C. § 353(g)(1)(C) (2022).

[83] *Combination Products FAQs*, *supra* note 81; O'Shea, *supra* note 80, at 653–54.

[84] U.S. FOOD & DRUG ADMIN., PRINCIPLES OF PREMARKET PATHWAYS FOR COMBINATION PRODUCTS: GUIDANCE FOR INDUSTRY AND FDA STAFF 8 (2022), https://www.fda.gov/media/119958/download.

biologic–device combination product.[85] Therefore, if the device portion fails to satisfy the regulatory requirements under the applicable abbreviated pathway, the combination product, as a whole, will fail to satisfy the criteria for approval as a generic or an interchangeable biosimilar, even though the drug (or biologic) component would have otherwise met the applicable regulatory requirements.

For a combination drug–device product seeking approval as a generic under an ANDA, the applicant must demonstrate therapeutic equivalence between the proposed generic combination product and the RLD (pioneer combination product). As discussed previously, an approved ANDA indicates the product is therapeutically equivalent to the RLD and listed as such in the Orange Book. Although reasonable for small-molecule drugs, this approach creates problems unique to many drug–device combination products. Firstly, FDA appears to be interpreting therapeutic equivalence, namely its requirement for safety, to mean that the user interface between the device parts of the two products must be similar enough such that in case of a substitution, the end user would be able to use either product without additional training or intervention by a healthcare provider.[86] Secondly, as currently defined, the bioequivalence requirement is very difficult to establish for drug–device combination products as these products commonly use complex formulation and/or delivery systems.[87] Establishing bioequivalence requires proof of equivalence in pharmacodynamics.[88] For instance, compared to orally administered small-molecule drugs, establishing pharmacodynamics equivalence between two inhalers, common examples of drug–device combination products, is significantly more challenging. Pharmacodynamics equivalence can be established with blood level analysis for many orally administered drugs; for inhalers, in addition to the required blood level analysis, measurements must be taken in the respiratory system, a considerably more difficult and costly task.[89] FDA has recognized this challenge and, in recent years, has published draft guidance on establishing bioequivalence for several drug–device combination products.[90] However, despite such guidance, required studies remain costly, tedious, and potentially clinically unnecessary.

For biologic–device combination products seeking approval as a biosimilar, among other stipulations, FDA's recent guidance documents specify that licensure under section 351(k) would not be possible if design differences in the delivery device component results in a "clinically meaningful difference between the proposed product

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[85] *Id.*

[86] Stephanie H. Choi, Yan Wang, Denise S. Conti, Sam G. Raney, Renishkumar Delvadia, Andrew A. Leboeuf & Kimberly Witzmann, *Generic Drug Device Combination Products: Regulatory and Scientific Considerations*, 544 INT'L J. PHARMS. 443, 443–44 (2018), https://doi.org/10.1016/j.ijpharm.2017.11.038.

[87] *See, e.g.*, *id.* at 443 (noting that due to the regulatory and scientific complexities of bioequivalence determination in combination products, FDA has published a number of guidances to aid the industry in determining the types of studies necessary to establish bioequivalence for such products).

[88] Irvin Mayers & Mohit Bhutani, *Considerations in Establishing Bioequivalence of Inhaled Compounds*, 15 EXPERT OP. ON DRUG DELIVERY 153, 153–54 (2018).

[89] *Id.* at 154.

[90] *See, e.g.*, U.S. FOOD & DRUG ADMIN., COMPARATIVE ANALYSES AND RELATED COMPARATIVE USE HUMAN FACTORS STUDIES FOR A DRUG–DEVICE COMBINATION PRODUCT SUBMITTED IN AN ANDA: DRAFT GUIDANCE FOR INDUSTRY (2017), https://www.fda.gov/media/102349/download.

and the reference product in terms of safety, purity, and potency."[91] However, in a separate guidance document, FDA further explains that it would hypothetically allow biosimilar approval even with design differences in the delivery device, including the user interface.[92] Specifically, FDA uses the example of a reference biologic product approved in a vial form (non-device) being used under the 351(k) pathway as basis for the approval of a biologic–device combination product, such as an autoinjector.[93] In such cases, the guidance document further explains that a separate application may be needed for the approval or clearance of the device component.[94] However, the guidance is silent on whether flexibility afforded to biosimilars would also be extended to interchangeables, the relevant standard used by substitution laws at the state level.[95] Hence, unless FDA employs a similar approach to approve interchangeable biosimilars (rather than just biosimilars), the benefit for patients at point-of-sale for substitution purposes will be nil.

VII. SOLUTIONS

There are multi-prong solutions to this problem involving FDA, the states, and prescribers. However, before describing these solutions, it is beneficial to briefly review the process under the current typical scheme for substituting combination products.

The prescriber issues a prescription for a combination product using a particular brand name (e.g., EpiPen). The prescription is presented to the pharmacist either physically or electronically. The patient's out-of-pocket cost is determined at the pharmacy based on the patient's insurance drug formulary or the cash price if uninsured. The pharmacist can inform the patient of available alternative combination products containing the same drug or biologic component with possible differences in the delivery device (e.g., Adrenaclick or Auvi-Q in lieu of EpiPen). Suppose the patient decides the prescription should be filled as written. In that case, there is a possibility that the patient, and the patient's insurance company, including the taxpayers in cases of government payers, overpaid for a product, which can lead to other financial consequences, with the most direct result being medication nonadherence.[96] Alternatively, the patient may decide the prescription should not be filled as written due to cost or any other factor. If the patient decides to instead proceed with an alternative option, and the alternative option is not automatically substitutable under state law, then the pharmacist has to contact the prescriber to obtain affirmative authorization for the substitution. It is unlikely that such authorization can be obtained

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[91] U.S. FOOD & DRUG ADMIN., PRINCIPLES OF PREMARKET PATHWAYS FOR COMBINATION PRODUCTS 16 (2022), https://www.fda.gov/media/119958/download (here citing 42 U.S.C. 262(i)).

[92] *See* U.S. FOOD & DRUG ADMIN., QUESTIONS AND ANSWERS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT: GUIDANCE FOR INDUSTRY (Sept. 2021), https://www.fda.gov/media/119258/download.

[93] *Id.*

[94] *Id.* at 6.

[95] Chana A. Sacks, Victor L. Van de Wiele, Lisa A. Fulchino, Lajja Patel, Aaron S. Kesselheim & Ameet Sarpatwari, *Assessment of Variation in State Regulation of Generic Drug and Interchangeable Biologic Substitutions*, 181 JAMA INTERNAL MED. 16, 17 (2020) ("State laws do not allow pharmacist substitution of biosimilar drugs and vary with their approach to interchangeable biologic substitution.").

[96] Aurel O. Iuga & Maura J. McGuire, *Adherence and Health Care Costs*, 7 RISK MGMT. & HEALTHCARE POL'Y 35, 37 (2014).

in real-time, leading to delay in care, possibly medication nonadherence, and adding to the pharmacist's and the prescriber's administrative burden.[97] It is worth remembering that insofar as it relates to combination products, the above scenario describes a situation where the drug or biologic component is otherwise substitutable. However, the substitution is prohibited because of differences, even minor ones, between the delivery device component of the combination products.

After obtaining affirmative authorization from the prescriber, then the pharmacist is required to provide the required counseling, including instructions on how to properly use the device component prior to dispensing the alternative combination product.[98] However, if the alternative combination product is substitutable under the state law, then the substitution can occur seamlessly, such as in states where substitution for epinephrine autoinjectors, regardless of FDA's therapeutic equivalence determination, is specifically allowed (see *infra* Section VII.B, on "Modifying State Laws").[99]

A. Less Stringent FDA Criteria

All states either mandate or permit the use of the Orange Book and the Purple Book as the basis for determining permissible substitutions under their respective substitution laws.[100] Consequently, one potential solution would be less stringent criteria for determining Orange Book and Purple Book designation of therapeutic equivalence (or interchangeability) by FDA, specifically for combination products. For drug–device combination products, at least for inclusion into the Orange Book as a therapeutic equivalent to an RLD, FDA could require only the establishment of therapeutic equivalence between the drug components of the drug–device combination product and the RLD. This would be analogous to FDA's approach as outlined in its guidance document for establishing biosimilarity in biologic–device combination products, where device component differences between the reference product and the biosimilar are permitted while keeping the standard of biosimilarity the same for the biologic component.[101] However, this tolerance is with the knowledge that biosimilars are generally not considered automatically substitutable. Nonetheless, it is a worthwhile option to consider.

As with any substitution, safety is a top concern. In particular, even minor differences between delivery devices can lead to the inability to use, or inappropriate use, by the patient who lacks sufficient training to appropriately use the substituted combination product, potentially leading to significant complications in case of

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[97] Alex J. Adams, *Prescription Adaptation Services: A Win for Patients and Providers*, 11 INNOVATIONS PHARMACY 1, 1–2 (2020).

[98] *See ASHP Guidelines on Pharmacist-Conducted Patient Education and Counseling*, AM. SOC'Y OF HEALTH SYS. PHARMACISTS (ASHP), https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/pharmacist-conducted-patient-education-counseling.ashx [hereinafter *ASHP Guidelines*].

[99] Ohio Rev. Code § 4729.382.

[100] *See* Vivian, *supra* note 50.

[101] *See* FDA, DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT, *supra* note 32.

need.[102] These complications can be severe, even fatal.[103] This concern can be alleviated by existing state and federal laws requiring pharmacists to provide training and counseling to patients when dispensing prescription medications.[104] Substitution does not alter these requirements. As described above, this is similar to the current model where, when substitution is not permitted under state law, the pharmacist must still provide necessary training after receiving affirmative authorization from the prescriber.[105] Therefore, a more permissive substitution scheme will not further burden the pharmacist or endanger the safety of patients beyond the current model.[106] It will, however, eliminate the need to obtain affirmative authorization from the prescriber in cases where the drug component is considered therapeutically equivalent and substitutable. This will decrease the cost to patients and payers and decrease the administrative burden of both the pharmacist and the prescriber while expediting patient care.[107]

Moreover, by updating the current "A" and "B" coding system of the Orange Book, FDA can alleviate any concerns regarding potential confusion as to which combination products are identical to their RLD versus ones with only the drug component being identical. For instance, FDA could consider adopting the letter "C" (or any other letter for that matter) to indicate that the drug component of a drug–device combination product is therapeutically equivalent to the RLD, while there may be differences in the delivery device component.

A similar approach can also be adopted for biologic–device combination products. FDA has already indicated its willingness to consider combination products under the 351(k) pathway if the biologic component meets the regulatory requirements for biosimilar designation, even if the delivery device component is different than the reference product.[108] This permissibility must also extend to interchangeable biosimilars to fully realize the benefits of substitution laws. It is also worth noting that the current regulations only require interchangeables to be able to be substituted "without the intervention of the *health care provider who prescribed the reference product*."[109] Arguably, a biologic–device combination product that is comprised of a biologic product component that is otherwise interchangeable with the reference product and only lacks that designation due to variation in the delivery device can be substituted safely. This can be accomplished with only the intervention of the dispensing pharmacist, not necessarily the "health care provider who prescribed the reference product,"[110] still meeting this regulatory requirement.

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[102] Thomas Weinhold, Marzia Del Zotto, Jessica Rochat, Jessica Schiro, Sylvia Pelayo & Romaric Marcilly, *Improving the Safety of Disposable Auto-Injection Devices: A Systematic Review of Use Errors*, 4 AM. ASS'N OF PHARM. SCIENTISTS OPEN 1, 2 (2018).

[103] *Id.*

[104] *See* Jesse C. Vivian, *Duty to Warn with No Directions for Use*, 37 U.S. PHARMACIST 60 (2012), https://www.uspharmacist.com/article/duty-to-warn-with-no-directions-for-use.

[105] *See ASHP Guidelines*, *supra* note 98.

[106] *See* Adams, *supra* note 97.

[107] *Id.*

[108] *See* FDA, DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT, *supra* note 32.

[109] 42 USC § 262(i) (emphasis added).

[110] *Id.*

However, traditionally, FDA has approached therapeutic equivalence determination and, to some extent, interchangeability, as an objective and scientific judgment, thereby differentiating this task from substitution authority which may involve social and economic policy administered by the states.[111] Coupled with FDA's mandate to stay clear of regulating the practice of medicine,[112] it is unlikely that the agency can successfully be persuaded to change its stance on these concepts.

B. Modifying State Laws

Alternatively, a more practical approach may be amending each state's generic substitution laws and regulations to expand the pharmacist's substitution authority, at least concerning combination products. After all, substitution laws are state-level laws.[113] Pharmacists, dubbed by some as "the most overtrained and underutilized" professionals in America, are uniquely positioned in this context to leverage their skills and knowledge to make substitution decisions when given expanded authority.[114] Allowing pharmacists to practice at the "top of their license" is crucial in realizing the full benefits of a team-based approach to patient care.[115] One step towards that goal is enabling pharmacists to take a more active role in substituting combination products. While empowering pharmacists to be more involved in substitution decisions is commonsense, preserving the prescribers' authority and patients' choice in prohibiting such substitution is paramount.

Several states, including Maryland, Minnesota, and South Carolina, have laws permitting the substitution of a drug product with its therapeutic equivalent based on a pharmacist's "professional opinion" or another variation of this term.[116] Notably, the

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[111] *See Orange Book Preface*, *supra* note 57.

[112] Wendy Teo, *FDA and the Practice of Medicine: Looking at Off-Label Drugs*, 41 SETON HALL LEGISLATIVE J. 305, 307–08 (2017) (citing ROBERT P. BRADY, FUNDAMENTALS OF LAW & REGULATIONS: AN IN-DEPTH LOOK AT FOOD & DRUG ADMINISTRATION MODERNIZATION ACT 423–24 (David G. Adams & Richard M. Cooper eds., 1st ed. 1997); Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) ("[T]he FDA's mission [is to] . . . regulate . . . without directly interfering with the practice of medicine")).

[113] *See* PASHA, *supra* note 62.

[114] Jennifer Kibicho, Steven D. Pinkerton, Jill Owczarzak, Lucy Mkandawire-Valhmu & Peninnah M. Kako, *Are Community-Based Pharmacists Underused in the Care of Persons Living with HIV? A Need for Structural and Policy Changes*, 55 J. AM. PHARMACISTS ASS'N 19, 19–30 (2015); Brian F. King, *Emerging Market for Biosimilars: State Legislation Should Reconcile Biosimilar Substitution Laws with Existing Laws on Generic Substitution*, 18 DEPAUL J. HEALTH CARE L. 31, 41 (2017); Albert I. Wertheimer, *The Underutilised Pharmacist*, 9 J. PHARM. HEALTH SERVS. RSCH. 77, 77 (2018); Earl L. Carter, *The Most Overtrained and Under Utilized Profession in America*, THE HILL (May 2, 2016), https://thehill.com/blogs/ballot-box/278414-the-most-overtrained-and-under-utilized-profession-in-america.

[115] Jason Ausili, *Why Pharmacists Need to Practice at the Top of Their Licensure*, PHARMACY TIMES (Sept. 16, 2021), https://www.pharmacytimes.com/view/why-pharmacists-need-to-practice-at-the-top-of-their-licensure.

[116] MD. CODE REGS. 10.09.03.05(4)(a)(i) (2023) ("A drug product in the same strength, quantity, dose, and dosage form as the prescribed drug which is, in the provider's professional opinion, therapeutically equivalent to the drug as prescribed"); MINN. STAT. §151.21 (2023) ("A pharmacist may not substitute a generically equivalent drug unless, in the pharmacist's professional judgment, the substituted drug is therapeutically equivalent and interchangeable to the prescribed drug."); S.C. CODE ANN. § 40-43-86 (2023) ("Upon receiving a prescription for a brand name drug or for a specific biological product, a registered pharmacist may in his professional judgment substitute an equivalent drug or interchangeable biological product as provided in this subsection.").

term "professional opinion" or its equivalent is not a license for the pharmacist to exercise independent judgment. For instance, the relevant statute in Minnesota was interpreted by the Minnesota Board of Pharmacy such that the pharmacist's "professional judgement" when substituting epinephrine autoinjectors requires a "legitimate and documented basis."[117] Although these laws seem more permissive at first glance, they generally preclude the substitution of combination products that do not meet FDA's definition of therapeutic equivalent, essentially relying on the same approach as the Orange Book for determining therapeutic equivalence.

At least three states—Ohio, Indiana, and Utah—have recently expanded the pharmacists' authority over substituting specific combination products. In January 2019, Ohio's governor signed a law permitting pharmacists to substitute epinephrine autoinjectors with generics that contain an identical form of epinephrine as in the autoinjector prescribed.[118] In July 2020, a similar law passed by Indiana's legislature became effective, permitting pharmacists to substitute epinephrine products with a therapeutic alternative, defined primarily as drug products with similar expected therapeutic effects.[119] Finally, in May 2020, a Utah amendment became effective, exempting the substitution of albuterol inhalers from the prior requirement for substitutes to be based on the Orange Book; instead, in consultation with the physician licensing boards in Utah, a more permissive substitution scheme was created specifically for albuterol inhalers.[120] However, as detailed above, these laws generally address the substitution of specific combination products. They do not address the need to allow substitution for other combination products. Extending this authority to encompass all combination products under a similar framework would be ideal and likely to pose minimal risk to patient safety.

Some scholars have advocated for even broader authority for pharmacists beyond simple substitution to include initiating and changing prescriptions in limited circumstances under the umbrella term Prescription Adaptation Services (PAS).[121] PAS refers to "the ability of a pharmacist to autonomously 'adapt' an existing prescription when the action is intended to optimize the therapeutic outcome," not dissimilar to the authority of pharmacists in other advanced countries.[122]

Moreover, organizations such as the American Legislative Exchange Council (ALEC) have taken steps to draft model legislation that states can adopt to allow for

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[117] *General FAQs*, MINN. BD. OF PHARMACY, https://mn.gov/boards/pharmacy/resourcesfaqs/faqs/generalfaqs.jsp (last visited May 5, 2023) ("a pharmacist is not required to use the Orange Book when making generic substitutions. However, pharmacists have to have some sort of basis for their 'professional judgment.' If the Orange Book is not consulted, or if the Orange Book does not list the generic as being therapeutically equivalent to the brand name product, the pharmacist should have some other, legitimate and documented basis for concluding that a drug is generically and therapeutically equivalent to the drug prescribed—and that it is safely interchangeable. If pharmacists do not have a documented basis for substitution, they should contact the prescriber for approval of the substitution and document this on the prescription.").

[118] Ohio Rev. Code Ann. § 4729.382 (West 2023); *Rep. Merrin's "Epinephrine Accessibility Act" Signed Into Law: House Bill 101 Addresses Concerns of Rising Cost of Epinephrine*, OHIO HOUSE OF REPRESENTATIVES, (Jan. 8, 2019), https://ohiohouse.gov/members/derek-merrin/news/rep-merrins-epinephrine-accessibility-act-signed-into-law-99007 (last accessed May 5, 2023).

[119] IND. CODE ANN. §§ 25-26-13-25.3, 25-26-16.5-4 (West 2023).

[120] UTAH CODE ANN. 58-17b-605 (West 2023).

[121] *See* Adams, *supra* note 97.

[122] *Id.*

broader prescription authority by pharmacists independent of a prescriber's authority.[123] Although the possibility has been formally explored by at least one jurisdiction (i.e., Vermont) to date, such broad legislation has not been adopted in any jurisdiction in the United States.[124] Such efforts conferring broad authority will likely be heavily opposed by physician organizations and other interest groups representing other professionals with current prescriptive authority as it will be viewed as too broad and encroaching on their respective professional areas of practice.[125]

C. Interventions Targeting Prescribers

Yet another method for addressing the shortcomings of substitution laws concerning combination products is changing habits at the prescriber level. Physician education, incentives, clinical decision support systems, and use of e-prescribing can all play a role.[126] Past studies have shown that educational interventions alone are effective in improving the knowledge of prescribers about generic medications, but results have been mixed in changing prescribing habits.[127] However, going beyond educational interventions and leveraging the inherent power of technology such as clinical decision support systems to address this particular concern is especially germane given the increased use of e-prescribing throughout the United States, partly in response to the Health Information Technology for Economic and Clinical Health (HITECH) Act and the meaningful use standards set by the Centers for Medicare and Medicaid Services (CMS).[128] It is theorized that e-prescribing can increase cheaper

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[123] *Pharmacist Prescribing Act*, AM. LEGIS. EXCH. COUNCIL, https://alec.org/model-policy/pharmacist-prescribing-authority-act/ (last accessed May 5, 2023) ("Pharmacists receive extensive training and education to evaluate, diagnose and prescribe medications to patients for a variety of medical conditions. This Act would empower pharmacists to utilize the full extent of their pharmacological expertise to prescribe certain low-risk medications to patients.").

[124] VT. SEC'Y OF STATE, OFF. OF PRO. REGUL., EVALUATION OF PHARMACIST PRESCRIBING AUTHORITY, https://legislature.vermont.gov/assets/Legislative-Reports/Act-30-Sec-15-Pharmacist-Prescribing-Authority-Report-v3.pdf (last accessed May 5, 2023).

[125] *Id.*; Magdalena Waszyk-Nowaczyk, Weronika Guzenda, Karolina Kamasa, Kornel Pawlak, Natalia Bałtruszewicz, Karolina Artyszuk, Artur Białoszewski & Piotr Merks, *Cooperation Between Pharmacists and Physicians—Whether It Was Before and is It Still Ongoing During the Pandemic?*, 14 J. MULTIDISCIPLINARY HEALTHCARE 2101, 2104 (2021) ("Family doctors are often not sure what role pharmacists play; they are opposed to extending their role because they would prefer to work under their authority."); Michelle Andrews, *Despite Doctors' Concerns, Pharmacists Get More Leeway to Offer Treatment with Testing*, KFF HEALTH NEWS (Mar. 31, 2022), https://kffhealthnews.org/news/article/pharmacists-test-and-treat-doctors-opposition/; Daniel Weiss, *AMA Opposes Giving Pharmacists Prescription Authority*, PHARMACY TIMES (July 10, 2012), https://www.pharmacytimes.com/view/ama-opposes-giving-pharmacists-prescription-authority ("The American Medical Association's House of Delegates has adopted a policy against allowing pharmacists to prescribe medication without oversight by or an order from a physician.").

[126] ASPE Staff, *Expanding the Use of Generic Drugs*, OFF. OF THE ASSISTANT SEC'Y FOR PLAN. & EVALUATION (Nov. 30, 2010), https://aspe.hhs.gov/reports/expanding-use-generic-drugs-0.

[127] William C. Wadland, Lynda Farquhar, Faith Priester, Kathleen Oberst & David P. Weismantel, *Increasing Generic Prescribing: A Resident Educational Intervention*, 37 FAMILY MED. 259, 262–63 (Apr. 2005); *Doctors Should Prescribe Generic Medications Whenever Possible Rather than More Expensive Brand Name Drugs*, AM. COLL. OF PHYSICIANS (Nov. 24, 2015), https://www.acponline.org/acp-newsroom/doctors-should-prescribe-generic-medications-whenever-possible-rather-than-more-expensive-brand-name.

[128] Amber Porterfield, Kate Engelbert & Alberto Coustasse, *Electronic Prescribing: Improving the Efficiency and Accuracy of Prescribing in the Ambulatory Care Setting*, 11 PERSPS. IN HEALTH INFO. MGMT. 1, 2 (2014).

drug use by making information about available generics, formularies, and cost information available to prescribers at the time of prescribing, with at least one study showing e-prescribing to increase generic drug use by 5.9%.[129] Another study has shown a 22% increase in generic medication prescriptions after implementing a generic substitution clinical decision support system within the e-prescribing software.[130]

However, reliance on e-prescribing alone has its downsides. Firstly, the cost associated with setup, maintenance, and transaction fees creates a barrier to universal adoption, risking inequities within the vulnerable population most in need of substituting lower-cost medications.[131] Nevertheless, CMS and state mandates have increased adoption rates.[132] More importantly, like any other software, clinical decision support systems are only as good as their underlying foundation and input data.[133] Due to the concerns discussed above about generic (or interchangeable) designation for combination products, there is no "official" single source of equivalencies to be adopted by software developers who often lack clinical training.

Furthermore, pricing information is often unavailable or inaccurately available to clinicians at the bedside.[134] Coupled with nuances of insurance coverage, including copays and deductibles, it is challenging to ascertain the actual cost to the patient for a given medication.[135] Therefore, the clinical decision support system cannot provide appropriate guidance. Even if pricing was to become available with a high degree of accuracy, adding yet another task to the clinician who is already under enormous time constraints to provide the appropriate standard of care is unwise.[136] Especially since this would be duplicative as the pharmacist must still check the price at the point of sale in order to collect appropriate payment prior to dispensing the prescribed medication.

Notwithstanding the above concerns, a workaround could include using more descriptive terms when prescribing combination products rather than brand names. For instance, prescribing *epinephrine autoinjector* instead of *EpiPen* or *albuterol inhaler* instead of *Proair*. Using more descriptive terminology would legally allow the

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[129] *See Expanding the Use of Generic Drugs*, *supra* note 10.

[130] Shane P. Stenner, Qingxia Chen & Kevin B. Johnson, *Impact of Generic Substitution Decision Support on Electronic Prescribing Behavior*, 17 J. AM. MED. INFORMATICS ASS'N 681, 684–85 (2010).

[131] Megan Ducker, Chelsea Sanchez & Shawn Riser Taylor, *Pros and Cons of E-Prescribing in Community Pharmacies*, 8 U.S. PHARMACIST 4, 4–7 (2013).

[132] Rahi Abouk & David Powell, *Can Electronic Prescribing Mandates Reduce Opioid-Related Overdoses?*, ECON. & HUM. BIOLOGY 1, 1–2 (2021) (Author Manuscript); *E-Prescribing*, CTRS. FOR MEDICARE & MEDICAID SERVS. (2022), https://www.cms.gov/Medicare/E-Health/Eprescribing.

[133] Wim Van Biesen, Daan Van Cauwenberge, Johan Decruyenaere, Tamara Leune & Sigrid Sterckx, *An Exploration of Expectations and Perceptions of Practicing Physicians on the Implementation of Computerized Clinical Decision Support Systems Using a Qsort Approach*, 22 BMC MED. INFORMATICS & DECISION MAKING 185, 91 (2022); Helen W. Wu, Paul K. Davis & Douglas S. Bell, *Advancing Clinical Decision Support Using Lessons From Outside of Healthcare: An Interdisciplinary Systematic Review*, 12 BMC MED. INFORMATICS & DECISION MAKING 90, 91 (2012);.

[134] Joey Mattingly, *Understanding Drug Pricing*, 37 U.S. PHARMACIST 40, 40–45 (2012); Mark T. Silvestri, Tasce R. Bongiovanni, Janis G. Glover & Cary P. Gross, *Impact of Price Display on Provider Ordering: A Systematic Review*, 11 J. HOSP. MED. 65, 65 (2016).

[135] *See* Mattingly, *supra* note 134; Silvestri et al., *supra* note 134.

[136] Justin Porter, Cynthia Boyd, M. Reza Skandari & Neda Laiteerapong, *Revisiting the Time Needed to Provide Adult Primary Care*, 38 J. GEN. INTERNAL MED. 147, 153 (2022).

pharmacist to dispense an appropriate product that falls under the prescription's terminology. Clinical decision support systems can play a significant role in assisting clinicians with switching prescription wording to preferred terms. Clinical decision support systems may be able to maintain their exemption from medical device classification and regulation by avoiding automatically switching the wording of the prescription.[137] However, these systems may suggest such a change to the prescriber at the time of prescribing.[138] A similar scheme can be devised for other comparable combination products. Still, it will likely require design and implementation at an institutional level, ignoring the underlying purpose for the existence of substitution laws in the first place and continuing to undervalue the pharmacist's role as an integral member of the clinical team.

VIII. CONCLUSION

Over the past five decades, substitution laws have facilitated exponential growth in the generic drug market share. However, these laws must be revised to be more permissive, especially concerning combination products. The current structure of substitution laws is a byproduct of a bygone era where the role of combination products was limited at best, and biosimilars did not exist as a product category. Momentum has been building behind expanding the substitution authority of pharmacists when deemed appropriate.[139] Some states have been more restrictive while others have taken a less rigid approach; still, others have implemented an innovative framework to address the ever more complex marketplace.[140] For those who worry that more permissive substitution could affect clinical decision-making or choice among patients, substitution laws have always allowed prescribers and patients to restrict or decline substitution.[141] This feature should stay the same. As states investigate updating their relevant substitution laws to conform to the realities of the 21st Century, the needs of the patient must take center stage.

If the goal is to serve the patient's needs best, there is no justification for continuing to allow the pervasive underutilization of pharmacists. As discussed above, pharmacists are capable professionals, and, if adequately empowered under state law, they can make substitution decisions beyond the current rigid framework employed in most states. This is especially true for combination products with identical drug or interchangeable biosimilar components. Focusing on more permissive substitution laws should not come at the cost of ignoring other interventions described above, including working with FDA and prescribers to optimize the role of these stakeholders. Finally, any safety risk to patients by allowing for more permissible substitution for

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[137] ASHLEIGH GIOVANNINI & AMIRALA S. PASHA, LAWS OF MEDICINE: CORE LEGAL ASPECTS FOR THE HEALTHCARE PROFESSIONAL 393–94 (Amirala S. Pasha ed., 1st ed. 2022) (positing that in order to maintain exemption from medical device classification, clinical decision support system must allow for independent review of the recommendation by the healthcare professional. Therefore, switching the wording of a prescription automatically without an affirmative action by the prescriber will most likely disqualify the system from being exempt from medical device regulations.).

[138] *Id.*

[139] Alex J. Adams, *Prescription Adaptation Services: A Regulatory and Practice Perspective*, 52 ANNALS PHARMACOTHERAPY 700, 700 (2018).

[140] *See* Vivian, *supra* note 50; *see* Adams, *supra* note 97.

[141] *See* Vivian, *supra* note 50.

combination products, given the preexisting requirement for pharmacists to provide appropriate counseling when dispensing medications, will be minimal. However, this practice would decrease administrative burdens, reduce costs, and expedite patient care.