TAKING BIOSIMILARS TO THE NEXT LEVEL: WHY FEDERALIZING THE SUBSTITUTION OF BIOSIMILARS PROMOTES INNOVATION, COMPETITION, AND PATIENT SAFETY

I. INTRODUCTION

At 71 years old, Philip DeLuca knows itôs no easy task keeping up with ten grandchildren.[1] While that would intimidate any grandparent, Mr. DeLuca finds it especially difficult to summon the energy to play catch or tag ð his bone marrow produces insufficient red blood cell amounts, making his blood less able to successfully transport oxygen throughout his body.[2]

Although weekly injections that boost his red blood cell levels have given him hope, the cost of a single shot is something to turn pale over ð $1,500.[3] His medication, Procrit, is part of a class of drugs called ñbiologics,ò[4] which are defined under the Public Health Service Act as any ñvirus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.ò[5] In other words, biologics are derived from other living organisms[6] and are used

1. *Whatôs Keeping Less Expensive Biologic Drugs From the U.S. Market?*, PBS NEWSHOUR (Apr. 19, 2014, 5:00 PM), http://www.pbs.org/newshour/bb/whats-keeping-generic-version-biologic-drugs-u-s-market.

2. *Id.*

3. *Id.*

4. *Id.*

5. 42 U.S.C. § 262(i) (2012).

6. Shawn P. Gorman et al., *The Biosimilars Act: The United Statesô Entry Into Regulating*

to treat various diseases or conditions in humans[7] such as rheumatoid arthritis, macular degeneration, and possibly even Alzheimerôs and cancer.[8]

Biologics tend to be so expensive, in part, because they are often composed of large molecules[9] that can only be produced through relatively complex[10] biological processes.[11] Accordingly, slight changes in the

generic drug manufacturerôs abbreviated new drug application (ANDA) if the applicant can demonstrate the drug is bioequivalent (identical) to an already-approved innovator drug[18] (the reference product) whose patent has expired.[19] This pathway has significantly reduced both the time[20] and money[21] it takes for a generic drug to safely reach the market, with savings passed onto consumers.[22]

Unbeknownst to a majority of the American public,[23] the 2010 Patient Protection and Affordable Care Act (ñAffordable Care Actò) has set the stage for patients like Mr. DeLuca to access essential biological medications at more feasible prices.[24]

The Affordable Care Act included a section called the Biologics Price

interchangeably when referring to the drug on which a generic chemical drug or biosimilar is based. ñGeneric drugò will refer to any chemical-based drug approved under the ANDA system.

Although the biosimilar approval pathway mirrors the well-established generic chemical drug pathway created under the 1984 Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Act,[29] biosimilars call for different regulations[30] than chemical drugs due to their unique compositions[31] and manufacturing processes.[32] For reasons that will be addressed later in this paper, a biosimilar may never be *completely*

completely identical to the innovator drug,[39] there is a growing concern that states may inappropriately apply laws designed to govern generic *chemical* drugs to biosimilars, sacrificing patient wellbeing in the process.[40]

This paper is divided into four sections. Section II will elaborate on the Biosimilars Act, its impact, and why biosimilars raise different issues than chemical drugs. Section III details the undesirable effects of leaving biosimilar substitution to the states and presents my thesis that a uniform, federal biosimilar substitution standard would promote innovation and competition while maintaining consumer safety. Finally, Section IV will dispel of concerns regBiosimi

chemical drug.[47]

drugs, biologics are more susceptible to failure at Phase III, which is the most expensive phase.[59] This is particularly worrisome because of the time, money, and resources already invested in the drug, only to have it fail at such a late stage.[60]

Although the FDA has not specified *exactly*

The FDAôs conservative ñrisk-based approachò[68] rates an applicantôs similarity to the reference drug along a continuum with designations of ñnot similar,ò ñsimilar,ò ñhighly similar,ò and ñhighly similar with fingerprint-like similarity.ò[69] Despite the purportedly conservative approach,[70] innovator drug manufacturers have been strongly urging the FDA to require that biosimilar applicants conduct their *own* clinical testing, and not rely solely on comparative data that uses the innovator manufacturerôs information.[71] While the FDA has only provided nonbinding guidance and recommendations on these matters,[72] the approved Zarxio application included data attained through its own testing.[73] Thus, the FDA may favor biosimilar applicants who have conducted independent testing and have not primarily relied on the innovatorôs data.[74]

Given the significant amount of time and resources devoted to getting a drug through the development pipeline,[75]

as five to ten chemical reactions, while a biologic may take as many as 5,000 to 10,000, resulting in a more expensive development process.[80]

This expense, however, is tempered by the high economic returns a successfully developed and marketed biologic brings.[81] A new chemical drug takes an average of sixteen years to break even.[82] In contrast, a biologic has been estimated to break even in only 12.9 years.[83] This is partly attributable to the greater potential (compared to a chemical drug) for discovering ñmultiple therapeutic interventions . . . in the biological cascade of proteins . . . [acting on] the same ultimate target,ò and ñnew indications associated with the same or related pathways.ò[84] These new uses would provide sufficient economic prospects that outweigh the costly and risky development process.[85]

In 2010, the top twelve biologic products in the United States generated combined sales of roughly $30 billion.[86] Further, the average peak sales of a biologic drug is $712.5 million,[87] and ñbiotechnology drugs are the fastest growing segment of new therapeutics,ò jumping from 4% in the period between 1982 and 1992 to 16% in the period between 1993 and 2003.[88] The biologic market (and biotech industry broadly) is ñrapidly expanding by any number of measures, including the quantity of approved products, the size of the market, and the importance of these drugs to the health of U.S. citizens.ò[89] The big prescription-benefit manager Express Scripts, Inc. estimated that the United States alone could save $250 billion in drug costs over the next ten years if eleven biosimilars that are currently in development get approved.[90]

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80. Malkin, *Challenges to the Development of a Biosimilars Industry in the United States*, *supra* note 71, at 3.

81. Grabowski, *Follow-on Biologics*, *supra* note 42, at 6.

82. *Id.*

Id.

A testament to the industryôs predicted expansion, the CEO of Swiss drug manufacturer Novartis AG expressed his belief that biosimilars will not cause ña big impactò until at least 2017,[91] despite the fact that in 2014 the companyôs biosimilar production unit, Sandoz, enjoyed around $514 million in sales, up 23% from 2013.[92]

This tantalizing expected growth in the biosimilar realm has lead to increased competition, even disagreement, between innovator and biosimilar manufacturers,[93] which Congress attempted to mitigate through the following Biosimilars Act provisions.

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application to the FDA ñ*shall* provide to the reference product sponsor a copy of the [biosimilar] application . . . and such other information that describes

been approved in the European Union, the lack of interchangeability provisions abroad has hampered biosimilar market share growth there.[142]

Aware of the significant research and development costs that may deter manufacturers from pursuing a biologic or biosimilar,[143] the FDA has incentivized manufacturers by awarding the first interchangeable biosimilar an exclusivity period[144] and providing a patent dispute system.[145] These incentives are likely substantial enough for biopharmaceutical firms to invest in developing interchangeable biosimilars.[146]

However, the Biosimilars Actôs distinction between biosimilar and interchangeable drugs creates ambiguity not present in the chemical drug scheme.[147] Chemical drugs that meet the FDAôs generic drug application requirements are typically considered ñinterchangeable.ò[148] Thus, a pharmacist may freely substitute a generic for a brand name, subject to any specific state laws.[149]

In contrast, a pharmacist may only substitute an innovator drug with a biosimilar if it has been deemed interchangeable.[150] And even if a drug meets the difficult standard of interchangeability, the Biosimilars Act left each state to enact its own laws for when and how a pharmacist may actually substitute.[151] This may lead to inconsistent interchangeability procedures,[152]

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142. Blackstone & Fuhr, Jr., *supra* note 77, at 12; *see* Barbara Mounho et al., *Global Regulatory Standards for the Approval of Biosimilars*, 65 FOOD & DRUG L.J. 819, 832-34 (2010). The reluctance of the E.U. and other countries to include a potential interchangeability designation arises from a fundamentally erroneous assumption that the same provisions and laws governing chemical drugs can successfully govern biologic drugs. The biosimilar landscape must be approached in light of the reality that biosimilars fall short of true bioequivalence. Accordingly, concepts such as automatic substitution applicable to chemical drugs should be amended, if not eliminated, in the biosimilar context in favor of policies icies l Z Z

medication access,[153] healthcare costs,[154] and regulation across the states.[155] In more human terms, unaffordable prices may prevent Mr. DeLuca from receiving his essential red blood cell-boosting medication, even though a similar patient would not face such a barrier across state lines.[156]

III. PROPOSAL FOR FEDERAL INTERCHANGEABILITY STANDARD

A. Problems With State Law Regulation

Regarding *generic chemical drugs*, state law determines whether or not substitution is mandatory, whether patient consent is required before substitution, and whether the prescriber must indicate if substitution is or is not acceptable.[157]

Though states have already implemented *generic* substitution laws,[158] the innate discrepancy between *biosimilarity* (between biosimilar and biologic) and *bioequivalency* (between generic and brand name chemical drug) renders this legal framework undesirable for biosimilars and calls for more stringent and consistent regulation.[159]

Inconsistent substitution practices between states, coupled with the necessarily high standards for biosimilarity and interchangeability, would likely affect consumersô access to biosimilars across state lines.[160]

For example, Indiana recently approved a biosimilar interchangeability bill allowing a pharmacist to substitute if 1) the FDA has deemed the biosimilar to be interchangeable; 2) the prescriber includes a ñmay substituteò instruction in the prescription; 3) the pharmacist informs the customer of the

substitution; 4) the pharmacist notifies the prescriber within five days of substitution; 5) a record is kept of the substitution for at least five years.[161]

The Biotechnology Industry Organization (BIO) commended Indianaôs Governor and Legislature, stating that the ñbill is a model for [biosimilar] legislation.ò[162] The bill comports with BIOôs biosimilar substitution principles as it ñputs patients firstò by ensuring transparency and communication, but also ñmaintains

The other important takeaway is the differing language used in each bill.[169] While this variance may seem inconsequential at first, even minor differences in phrasing such as the affirmative ñmay substituteò or negative ñdo not substituteò can affect prescribing tendencies.[170] Formats that make it

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reinforces the positive view that biosimilars are safe and effective when dispensed properly.[198]

Requiring the preventative language (i.e. ñdispense as writtenò or ñdo not substituteò) frequently used with chemical drugs[199] may not only give the impression that biosimilars are not to be trusted, but would also likely make it easier for physicians to prohibit biosimilar substitution.[200] Such ease of prohibiting substitution is associated with significantly reduced generic drug use.[201] On the other hand, the affirmative ñmay substituteò promotes biosimilar use,[202] but prevents over-substitution through the reversed presumption and opt-in protocol.[203]

Moreover, this provision does not conflict with the Biosimilars Actôs language that an interchangeable biosimilar may be substituted ñwithout the intervention of the healthcare provider.ò[204] The prescribing doctor preemptively opts in, authorizing the pharmacist to substitute the prescription without any further permission or ñinterventionò needed from the prescriber.[205] Once a prescriber signs off on substitution when writing the prescription, the pharmacist need only provide *notice* to the prescriber and patient if a substitution *actually occurs*, not permission when actually performing the substitution.[206]

3. Notice, Not Consent, Is Mandatory

Notice to both patients and physicians should be mandatory, but not patient consent, because it significantly reduces substitution rates when

198. *See* BIOTECHNOLOGY INDUSTRY ORG., BIO PRINCIPLES ON PATIENT SAFETY IN THE SUBSTITUTION OF BIOLOGIC PRODUCTS, *supra* note 163.

199. *See* Wheaton, *supra* note 192.

200. *See id.*; *see* MASSON & STEINER, *supra* note 152, at 89.

201. M

required.[207] This in turn drives up costs for both consumers and healthcare systems.[208] States that require patient consent for generic drug substitution have experienced substitution rates 25% lower than those without such requirements.[209] Further, eliminating consent requirements could save more than $100 million in Medicaid coverage expenses.[210] Laws requiring consent may increase undue patient anxiety towards biosimilars (and generics) and deter their use.[211] This ultimately forces individuals, employers, and taxpayers to shoulder higher healthcare costs.[212]

The lack of mandatory patient consent does not preclude the normal dialogue between prescribing physician and patient, as well as patient and pharmacist, in which the patient may still choose the innovator drug over the biosimilar.[213] This proposed protocol would still require that the patient and prescriber receive notice of a substitution,[214] and that all parties involved make a well-informed decision with patient health as the priority. In fact, eighteen pharmaceutical companies, including Hospira, Actavis, Amgen, Genentech, and Sandoz, all support such a notice requirement.[215]

In 2010, the Congressional Budget Office estimated that a well-implemented biosimilar system could save the federal government between $9 billion and $12 billion over ten years.[216] More recently, Express Scripts estimated that the first two biosimilars expected to enter the U.S. market would save *patients and insurers* around $22.7 billion in healthcare costs over the first ten years.[217] Thus, requiring consent would undercut the systemôs efficiency and savings.[218]

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207. EXPANDING THE USE OF GENERIC DRUGS, *supra* note 22, at 7-8; *see* LEIGH PURVIS, AM. ASSôN OF RETIRED PERS. PUB. POLICY INST., A SENSE OF DÉJÀ VU: THE DEBATE SURROUNDING STATE BIOSIMILAR SUBSTITUTION LAWS 2 (2014).

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within an Art Group who ñroutinely examine patent applications from competitors regarding highly similar subject matter,ò which has not been found to misappropriate trade secret protection or infringe patent rights.[245]

Lastly, while the Freedom of Information Act allows any member of the public to obtain access to federal agency records,[246] the information submitted to the FDA by both biologic and biosimilar applicants is protected by ñExemption 4,ò which precludes disclosure of trade secrets.[247]

The Biosimilars Actôs prohibition against public disclosure, the FDAôs strictly internal use in promoting the public good, state trade secret laws, and judicial respect for trade secrets all should allay drug manufacturersô concerns about providing their information to the FDA and avoid trade secret misappropriation issues.[248]

B. 5th Amendment Takings

In April 2012, pharmaceutical company Abbott Laboratories filed a citizen petition requesting that the FDA not accept for filing, file, approve, or take any action indicating the agency would consider, a biosimilar application based on one of the companyôs biologics, Humira.[249] Abbott based its request on the 5th

Public policy[262] also demands the use of the proprietary information to ensure applicants meet the necessarily high standards[263] of biosimilarity and interchangeability. The public policy consideration of maintaining medication quality, safety, potency, and efficacy is paramount.[264] Any minor trade secret limitation (again, only for internal FDA use) is justified, particularly in light of the economic benefits provided through the exclusivity periods.[265]

V. CONCLUSION

On March 6, 2015, the FDA approved Sandozôs Zarxio, a biosimilar of Amgenôs filgrastim biologic that boosts the weakened immune systems of cancer patients undergoing chemotherapy.[266] Express Scripts has estimated that over the next ten years, Zarxioôs introduction in the United States may save $5.7 billion in drug costs.[267]

Further, in September 2015, the Federal Circuit denied Amgenôs attempt to extend its July 2015 injunction against Zarxio,[268] essentially lifting the injunction[269] and paving the way for Sandoz to market the first biosimilar in the United States.[270] While Zarxio isnôt expected to fully penetrate the market

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262. *See* 3 MILGRIM & BENSEN, *supra* note 237, at 12-20.2 to 12-20.3.

263. Kanter & Feldman, *supra* note 153, at 74; *see* MARGARET HAMBURG, FOOD & DRUG ADMIN., *supra* note 70.

264. BIOTECHNOLOGY INDUSTRY ORG., BIO PRINCIPLES ON FOLLOW-ON BIOLOGICS, *supra* note 34.

265. *See* 3 MILGRIM & BENSEN, *supra* note 237, at 12-20.2 to 12-20.3 and accompanying text.

266. Rockoff & Loftus, *supra* note 69; Noonan, *FDA Approves Sandoz Filgrastim Biosimilar*, *supra* note 11 (noting, however, thadoz FKA HQ¶VLQMXQFWLRQZDVHYHQWXDOOJUDQWHGEHFDXVH6DQGR failed to provide its biosimilar application and informadion).

267. Tavernise & Pollack, *supra* note 90.

268. *Federal Circuit Denies Amgenôs Emergency Motion for a Temporary Injunction in*

for one to five years,[271] these moves by the FDA,[272] the Federal Circuit,[273] and biopharmaceutical manufacturers[274] nonetheless are promising indications that the biosimilar market may be ready to take flight domestically.

Despite the biotech industryôs position at the forefront of advances in science, health, and business, the legal sector appears to be struggling most to keep pace with these developments. The idea that a biosimilar system cannot exist in the United States is based on the mistaken belief that laws governing chemical drugs should apply to biologic drugs. Eschewing the substitution practices traditionally used for generic chemical drugs would avoid the inertia threatening to inhibit the industryôs growth and prevent the benefits of affordable breakthrough medications from reaching patients.

Federalized substitution standards such as those set forth in this article would incentivize drug manufacturers to create interchangeable biosimilars that pharmacists would more readily substitute in place of a pricier biologic. Failure to account for the differences between biologic and chemical drugs, as well as the greater variance between an innovator biologic drug and biosimilar, would likely lead to inconsistent biosimilar substitution laws between states, disparate substitution practices by doctors and pharmacists, unequal medication access for patients, and increases in healthcare spending.

Yet, one cannot forget the human impact, because at its most fundamental level, the implementation of a successful biosimilar system means patients across the country, like Mr. DeLuca, can worry less about how they will survive paying exorbitant medical bills, and more about how they will survive keeping up with ten grandchildren.[275]

*Daniel Kadin**

271. *Id.*

272. *See* Rockoff & Loftus, *supra* note 69.

273. *See Federal Circuit Denies Amgenôs Emergency Motion for a Temporary Injunction in* Amgen v. Sandoz, *supra* note 268.

274. Noonan, *Sandozô NEUPOGENÈ Biosimilar Now on the Market*, *supra* note 270.

275. *Whatôs Keeping Less Expensive Biologic Drugs From the U.S. Market?*, *supra* note 1.

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