Biosimilar uptake in the United States: Examining state-level longitudinal trends in biosimilar filgrastim use and their association with biosimilar substitution policies

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2020

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Pharmacy

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Abstract

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Defined as medicines manufactured in a living system, biologics have demonstrated high clinical utility for an array of therapeutic areas. Due to their complex structure and sensitivity to manufacturing processes, it is extremely challenging to develop an exact copy of a biologic—as is possible with small molecule pharmaceuticals. Instead, a similar agent, known as a biosimilar is developed, which demonstrates equivalent effectiveness and safety as the reference brand[3]. Recognizing the need for increased affordability of promising biologic therapies, many countries have established approval pathways for biosimilars with the aim of reducing the price of biologics through increased market competition. Once a biosimilar is approved by the FDA, individual states can influence the uptake of the products through legislation at the state level. In addition to decentralized policies on biosimilar use, additional factors may impact product use such as disease

epidemiology for biosimilar-related indications, varying payer practices on biosimilar coverage and reimbursement. Understanding if and why states differ in their biosimilar use can potentially move us towards optimal uptake, reducing costs and improving patient access to biologics. This quantifies biosimilar filgrastim uptake ratios at the state level, uses longitudinal trends to examine the presence of state sub-groups based on product use, and finally assesses the association between the status and content of state-level biosimilar substitution legislation and biosimilar uptake. While biosimilars hold strong potential to decrease health system costs for powerful biologic therapies, their true cost-savings impact may depend on their uptake throughout the U.S. and this study will provide helpful insight on anticipated uptake trends and the association of policy levers with biosimilar use.

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ACKNOWLEDGEMENTS

I would like to acknowledge the guidance of Professor Lou Garrison, in addition to the guidance of my dissertation committee members.

DEDICATION

This dissertation is dedicated to my family members, partner, friends, and mentors who have all been a crucial part of this work.

Chapter 1. STATE-LEVEL BIOSIMILAR FILGRASTIM UPTAKE TRENDS IN THE UNITED STATES

1.1 INTRODUCTION

In recent decades, new biologic therapies have significantly improved the health of patients, particularly those with cancer or other chronic conditions. Unlike small molecule drugs, biologics are manufactured within a living system. While this process has yielded high clinical utility for an array of indications, it also incurs a larger research and development (R&D) cost—approximately $40 to $300 million USD and up to five years whereas small molecule R&D costs range from $2 to $5 million USD and up to 3 years[1]. The daily average price of biologics in the U.S. is $45 compared to $2 for small molecule drugs[2].

As many biologic therapies are reaching patent expiry in the U.S., the possibility of market competition driving down high prices may be realized. The introduction of generic equivalents to small molecules helped to reduce related drug prices through such market competition[3]. However, unlike small molecules, it is extremely difficult to create an exact copy of a biologic. Instead, a biosimilar, which demonstrates equivalent effectiveness and safety as the reference biologic, is developed[4].

Several countries have recognized the need to establish approval pathways for biosimilars, with the ultimate aim of both reducing prices and increasing access to the promising therapies[2,5–7]. Within the European Union (EU), where biosimilars have been available since 2006, the European Medicines Agency provides regulatory approval of biosimilars followed by country-specific policies and contracting. Experience with biosimilars in Europe suggests a 25-30% price discount for biosimilars relative to their reference biologics; although the price discounts are highly variable across product type and country, ranging from 2% to 80%[7,8] Different patterns of product use have also been observed between member countries[3,8,9]. Several factors may be associated with such price and use differences, including country-level reference pricing, reference biologic response to biosimilar entry, payer structures, and country-level biosimilar substitution laws[8].

The United States developed an abbreviated approval pathway through the Biologics Price Competition and Innovation Act of 2009 (BPCIA) for products that are highly similar to an FDA-approved reference biologic[10]. The first designated biosimilar to reach the U.S. market in 2015 was filgrastim, a biologic with a primary indication to reduce febrile neutropenia in cancer patients receiving myelosuppressive anti-cancer treatment[11,12]. Once a biosimilar is approved by the FDA, states can influence the uptake of the products through legislation at the state level. In addition to state laws on biosimilar use, additional factors may impact product use such as disease epidemiology for biosimilar-related indications and varying payer practices on biosimilar coverage and reimbursement[13–17].

The first biosimilar approval following the BCPIA in the United States is Zarxio ®, a biosimilar for filgrastim (Neupogen ®). In fact, there are four key filgrastim-containing biologics in the United States. Filgrastim (Neupogen®) was approved by the FDA in 1991 for five indications, peg-filgrastim (Neulasta®) is a second-generation drug approved by the FDA in 2001 for two indications (a subset of the five indications for filgrastim) and requires only one injection per treatment cycle whereas filgrastim requires several administrations per cycle[18]. In 2012 tbo-filgrastim (Granix®) received FDA approval through the Biologics Licensing Act and, although not defined as a biosimilar to filgrastim by regulatory agencies, it is approved for the same primary indication (febrile neutropenia in patients receiving myelosuppressive anti-cancer drugs)[19]. Under the BCPIA, filgrastim-sndz (Zarxio ®) was approved by the FDA in 2015 as the first biosimilar in the United States, and received approval for all five indications of the reference biologic filgrastim[20]. In order to understand the uptake of biosimilars and their dynamic impact in the United States, this analysis encompasses the use of all four filgrastim-containing products relevant to the market.

With the likely increase in biosimilar approvals in U.S., it is important to assess patterns of product use and key trends both nationally and at the decentralized, state level. By understanding if states differ in their biosimilar use and why, we can potentially move towards increased uptake of these products and more closely achieve their promise of reducing average biologic prices and improving patient access to biologics. This study provides insight into differential state trends in biosimilar filgrastim product use and associated trends in average payments to augment this understanding.

1.2 METHODS

Using the IBM Watson MarketScan® Databases, data were abstracted from 2010-2017 for each medical benefit claim of filgrastim (Neupogen®), tbo-filgrastim (Granix®), filgrastim-sndz (Zarxio®), and peg-filgrastim (Neulasta ®) administered during both outpatient and inpatient services. The IBM Watson MarketScan ® Databases link claims data to information regarding patient encounters with the healthcare system, including utilization and expenditures across various treatment settings[21]. While the databases include information for a variety of payers, including employers and health plans, it is primarily representative of the private healthcare coverage in the United States.

Eligible patients were identified as those receiving at least one claim with any of the four filgrastim-containing biologics noted above between 2010-2017. Utilization of biosimilars is measured as a use ratio, with total patients receiving biosimilar filgrastim (filgrastim-sndz) as a numerator and the total number of patients who use any filgrastim-containing product as a denominator in each month and state. Thus, “subjects,” or the units of analysis in this study, are states rather than patients. Use trends are considered relative to a market with all four filgrastim-containing biologics to capture shifting trends of second-generation biologic use, as more patients potentially shift from using filgrastim to its peg-filgrastim substitute.

In addition to utilization measures, covariates used in assessing payment trends aim to adjust for observable changes over time in the study population that can influence costs and payments. These covariates consisted of: total eligible population size which is included as a log transformation of total eligible population for each state and time period in the model, fraction of total biologic claims that are second generation peg-filgrastim, mix of payer type defined as a percentage of eligible population covered by PPO for each state and time period, average age of males and females separately within the eligible population for each state and time period, percentage of the population that is male for each state and time period, comorbidity index defined as the proportion of the eligible population with various comorbidity scores , assessed by Agency for Healthcare Research and Quality (AHRQ) algorithm for Elixhauser comorbidity index based on ICD-9 and ICD-10 codes[22–24]. By controlling for the fraction of second-generation peg-filgrastim, we are focusing on the share of biosimilar use among groups with similar fractions of second-generation use. The comorbidity score takes into account patient comorbidities within six months of the date for a qualifying claim, and summarized at the patient level.

In the overall dataset, patients with missing enrollment identification numbers were excluded (4.9% of patients) along with biologic claims that did not have any associated cost (<1 of biologic claims). Lastly, in the final analysis, states with low sample sizes (<10) for at least 50%

of the months in the study timeline were excluded, which lead to the exclusion of one state (Hawaii).

Latent class modeling uses statistical techniques to identify unobserved subgroups within a population based on an observed set of characteristics. For longitudinal data, an additional approach to latent class modeling considers the trend, or growth, of an observed variable for study subjects over time. Latent class mixed modeling (LCMM) is a method that can be used to identify unique groups within a population based on the trend of subjects' time-varying outcome measure[25–27]. LCMM is a subject-centered approach which focuses on the classification of subjects (i.e. states) based on their similarity to each other in an observed growth outcome of interest, rather than restrict an analysis to selected observable variables that are used in variable-centered models. Subject-centered approaches allow assessment based solely on the hypothesis of heterogeneity among subjects. This approach has been applied in a variety of healthcare research settings including alcohol use in young adults, cognitive declines among the elderly, and post-treatment prostate cancer progression[3,4] Using LCMM as a primary analytic approach, a latent class model was performed on the outcome variables of use ratio, as previously defined. Subjects in the analysis are states, and time periods considered are months from September 2015 (when filgrastim-sndz Zarxio ® initially reached the U.S. market) to December 2017 (end of the dataset). The LCMM model classifies states into a number of use-specified latent classes based on the behavior of a defined outcomes variable (biosimilar use). Model fit was assessed by Bayesian Information Criteria (BIC) and log-likelihood. The model with the strongest fit that retained at least 10% of the subjects in each class was selected.

Along with state-level use of biosimilar filgrastim, a key question of interest is how biosimilar filgrastim use is associated with average payments for all filgrastim-containing biologics. We conducted a descriptive analysis of average biologic filgrastim payment trends during two periods (before and after biosimilar marketing) by latent class using an interrupted time series analysis, with latent classes included as dummy variables in the models relative to Class 1. The primary outcome of interest in this analysis was to understand the growth rates of payments over time within each identified latent class and to determine if and how the introduction of biosimilars impacted the growth rate of average biologic payments. In order to identify these trends, the model captured coefficients for the time period, introduction of biosimilar filgrastim, and interaction among both of these variables and each latent class.

1.3 RESULTS

Initial identified data included 1,454,579 claims for one of the four noted filgrastim-containing biologics products. Claims with missing data on enrollee identification and payment were excluded from the analysis, resulting in 1,383,742 claims in the final dataset which is summarized below by period before and after biosimilar filgrastim was marketed (September 2015):

Table 1.1 Summary of claims analysis dataset (Total all years: 2010-2017)

Table 1.1 Summary of claims analysis dataset (Total all years: 2010-2017)

Characteristic	Jan 2010 to Sept 2015	Sept 2015 to Dec 2017
Total unique claims	1,166,678 claims	217,068 claims
Total unique patients	514,055 patients	111,383 patients
Biologic claims		
Filgrastim	474,676 (40.7%)	46,323 (21.3%)
Peg-filgrastim	682,868 (58.5%)	135,613 (62.5%)
Tbo-filgrastim	9,133 (0.7%)	16,696 (7.7%)
Filgrastim-sndz	0 (0.0%)	18,159 (8.5%)
Average age	51.7 years	51.8 years
Male	51.8 years	51.3 years
Female	51.7 years	51.9 years

Male patients	154,731 (30.8%)	32,301(29.0%)
Patient Elixhauser Score		
Score of 0	91,456 (17.8%)	11,600 (10.4%)
Score of 1	298,089 (58.0%)	59,080 (53.0%)
Score of 2	78,262 (15.2%)	24,753 (22.2%)
Score of 3	24,961 (4.9%)	8,641 (7.8%)
Score of 4	11,282 (2.2%)	4,065 (3.6%)
Score of 5+	10,005 (1.9%)	3,247 (2.9%)
Patients covered by PPO	334,135 (65.0%)	65,716 (59.0%)

Data for all patients were summarized to provide a filgrastim biosimilar use ratio (patients receiving biosimilar filgrastim/all patients receiving any of the four included filgrastim-containing biologics) per month and state. Table 1.2 shows three potential latent class models. The best performing model that retained at least 10% of all states in each class was the a model using beta link and three latent classes (named LCMM-beta-3C below).

Table 1.2 Latent class mixed modeling (LCMM) model fit assessment

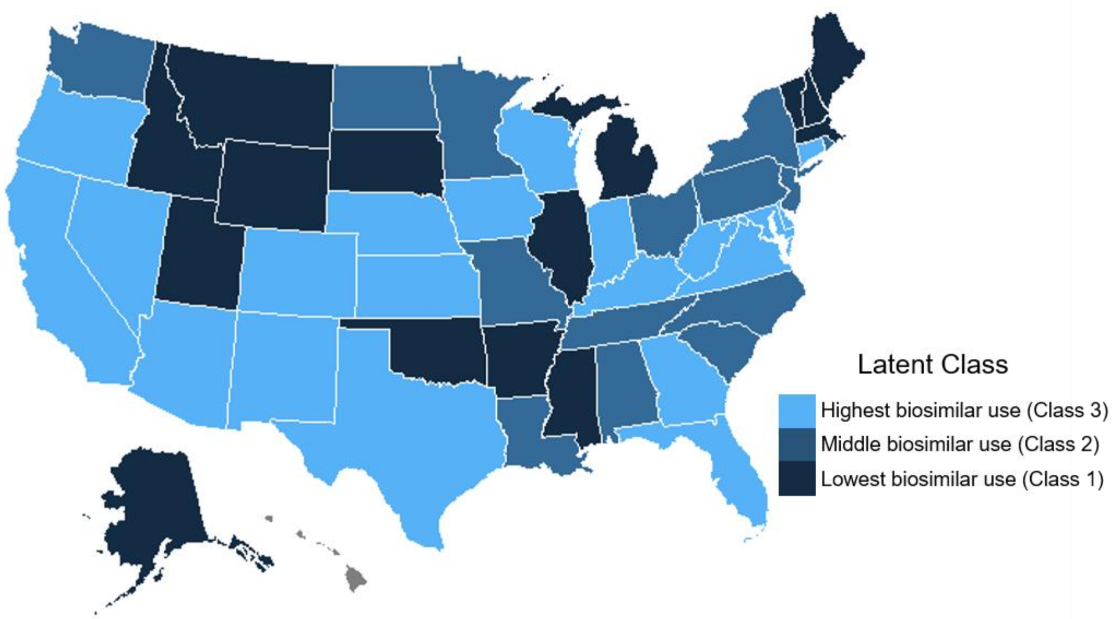
Table 1.2 Latent class mixed modeling (LCMM) model fit assessment

Model Name	LL	BIC	Link	Classes (n)+
LCMM-beta-2C	1751.54	-3472.29	Beta	2
LCMM-beta-3C	1758.12	-3473.89	Beta	3
LCMM-beta-4C	1759.68	-3465.45	Beta	4

+note: models with greater than four classes lead to less than 10% of states in some classes and were eliminated

The selected LCMM contained three classes of states, based on their utilization trends of biosimilar filgrastim from September 2015 through December 2017. A summary of states' classifications is provided in Figure 1.1 below. We see that states have a somewhat even distribution, with 41% belonging to the highest latent class 3 with greatest biosimilar filgrastim use, 28% belonging to latent class 2, and 31% belonging to latent class 1 with the lowest biosimilar use. Specific clusters of latent class appear to be located in the west (Class 3) and east (Class 2).

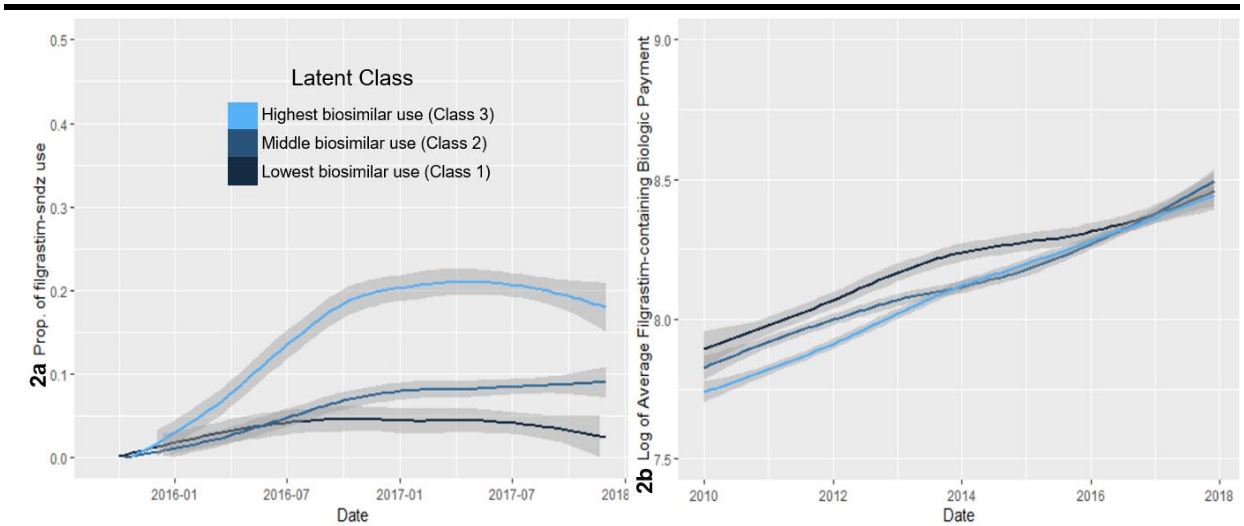
Class 3 (highest biosimilar use)	Class 2	Class 1 (lowest biosimilar use)
States (n): 20* States (%): 40.82% PP: 0.8871 AZ, CA, CO, CT, DE, FL, GA, IA, IN, KS, KY, MD, NE, NM, NV, OR, TX, VA, WI, WV	States (n): 14* States (%): 28.57% PP 0.7533 AL, LA, MN, MO, NC, ND, NJ, NY, OH, PA, RI, SC, TN, WA	States (n): 15* States (%): 30.62% PP: 0.8952 AK, AR, ID, IL, MA, ME, MI, MS, MT, NH, OK, SD, UT, VT, WY



PP: Posterior probability for states belonging to each class
* Data for Hawaii were dropped due to a small sample size.

Figure 1.1 Latent class summary and U.S. state classification map

Smoothed average uptake trends for each latent class in Figure 1.2 help visualize differences in the use of biosimilar filgrastim in each class relative to the full market (containing both filgrastim and peg-filgrastim). We see that Class 3 has the fastest biosimilar filgrastim uptake rate, while Class 1 has the lowest use of biosimilar filgrastim. While Class 2 trends are similar to Class 1 at the beginning of the time period, they increase and significantly surpass Class 1 by the start of 2017. In Figure 1.32, trends in the natural log of average claim payments over time for filgrastim-containing biologics are shown from January 2010 (one year prior to biosimilar introduction) to the end of the study period. Results of the model assessing growth rate in average payments among latent classes before and after the introduction of biosimilars is summarized in Table 1.3.



**trends are smoothed loess fits optimized for the dataset, grey area represents 95% confidence intervals*

Figure 1.2 Average smoothed uptake trends of biosimilar filgrastim by latent class

Table 1.3 Average payment model results

Table 1.3. Average payment model results

Variable	Value	SE	p-value
Intercept	7.820	.2160	< .0010
Time period	.0090	.0005	< .0010
Biosimilar period	.0539	.1560	0.7295
Time period * Biosimilar period	-.0026	.0020	0.1941
Latent Class 2	.0103	.0267	< .0010
Latent Class 3	-.0026	.0245	0.9152

Time period * Latent Class 2	-.0038	.0009	< .0010
Time period * Latent Class 3	-.0018	.0006	0.0045
Biosimilar period * Latent Class 2	-.0387	.2170	0.0748
Biosimilar period * Latent Class 3	-.0124	.1990	0.5338
Time period *Biosimilar period * Latent Class 2	.0072	.0027	0.0085
Time period *Biosimilar period * Latent Class 3	.0033	.0025	0.1819
Additional Covariates			
Age female	.0054	.0010	< .0001
Age male	.0112	.0015	< .0001
Sex	-.2090	.0535	< .0001
Log population	-.0144	.0062	0.0223
Insurance type (% PPO)	-.1770	.0256	< .0001
Elixhauser score 0 (% patients)	-.9760	.1940	< .0001
Elixhauser score 1 (% patients)	-.6390	.1930	< .0010
Elixhauser score 2 (% patients)	-.7620	.2060	< .0010
Elixhauser score 3 (% patients)	-.4940	.2060	0.0241
Elixhauser score 4 (% patients)	-.3060	.2380	0.1982
Use of 2nd gen product (% patients)	.0001	.0001	0.3870

From the results in Table 1.3, we see that during the pre-biosimilar filgrastim period (2010 – September 2015), filgrastim-containing average biologic expenditure grew at the rate of .90% per month in Class 1 states, which have the lowest utilization of the biosimilar . However, during the same time, average filgrastim-containing biologic expenditure grew at a significantly slower rate in Class 2 (0.9 – 0.4 =~ 0.5%) and class 3 (0.9 - 0.2% ~ 0.7%) states.

After the introduction of biosimilar filgrastim, there was no significant immediate shock or change on the growth rate for average payments in Class 1 states. The immediate shocks were also not significant for class 2 (p=0.952) and class 3 states (p=0.117), they were also not statistically different from the estimated shock in Class 1 states. For Class 2 states, the growth rate in expenditure seems to have increased in post biosimilar period, when the growth rate in expenditure was 0.95% compared to .5% in the pre period, a statistically significant difference with p<0.01. On the other hand, for Class 3 states, the growth rate in average payments seems to be similar in the pre-biosimilar and post filgrastim biosimilar introduction periods, p=0.134.

1.4 DISCUSSION

The analysis yielded key findings in understanding state-level uptake of biosimilar filgrastim and growth rates of filgrastim-containing average biologic payments before and after the introduction of biosimilars. Using LCMM, we determined that certain groups of states exhibited comparable patterns of biosimilar uptake. In identifying three distinct groups, or classes, of states based on their biosimilar-filgrastim, our subject-centered approach provides a foundation for investigating characteristics of states observed to have the highest biosimilar use, middle biosimilar use, and lowest biosimilar use.

Furthermore, this classification allows us to explore growth rates in average biologic payments, within each identified class of states. In our analysis, we aimed to understand any difference in the growth rate of average payments experienced by each identified class of states and how the introduction of biosimilars impacted these rates.   Our payment model revealed that the class with the lowest biosimilar use (Class 1) has the highest growth rate prior to the introduction of biosimilars. This indicates that Class 2 and Class 3 states were more cost-conscious than Class 1 states, even before the introduction of biologics. Therefore, it is not surprising to find that adoption of biologics were much faster in Class 2 and Class 3 states compared to Class 1 states.

After the introduction of biosimilar filgrastim, there was no significant immediate shock or change on the growth rate for average in Class 1 states. This result is expected as the adoption of biologics was minimal in these states. While our results suggested that states that adopted biosimilars more aggressively had slower growth rates in expenditures to begin with, adoption of biosimilars were not associated with a further slowdown in the growth of average biologic payments. In fact, in Class 2 states, there seems to be a slight increase in the growth rate in average payments during the post-biosimilar time period. This trend may be explained, in part, by the minimal adoption of biosimilars in Class 2 states, which reached a peak of only ~10% of the market by the end of 2017. During the same time period, Class 2 states increased their use of the second generation and more costly peg-filgrastim by approximate 7-10%. In contrast, we see that Class 3 states increased biosimilar use while maintaining a constant, lower percentage of peg-filgrastim use than either Class 2 or Class 3 states. Essentially, while Class 2 states used biosimilars more readily than Class 1 states, that use is not offsetting other forces that might be driving up costs. Such forces include the industry actions or selective shifts in prescribing patters that disproportionately impact Class 2 states more than in states in other classes, or selective shifts in prescribing and treatment patterns for those states.

Key findings from our analysis demonstrated the existence of related uptake trends within groups of states in the U.S. We further found that states more prone to use biosimilars at a higher rate were those that already experienced low growth rates in biologic filgrastim payments prior to the introduction of biosimilars. No significant impact on average payment growth rate was seen at the time of biosimilar introduction for all groups of states.

As various stakeholders are examining how to reduce overall spending in biologics through the lever or biosimilar competition, this analysis lends a few key insights: 1) not all states have been acting similarly in their uptake of biosimilar filgrastim and it remains essential to continue to investigate heterogeneous trends; 2) biosimilar uptake alone at its current level does not appear to be associated with a significant decrease in average payments for filgrastim-containing biologics; and 3) additional trends such as the increased use of second-generation peg-filgrastim may counteract or outweigh the cost reduction impact of biosimilar use in some states. In order to examine these trends further, addition research can be done in industry actions that shape the market (such as promotion of peg-filgrastim or selective targeting of specific payer networks). Additionally, work can be expanded to determine if these same findings are observed in other biologics groups aside from filgrastim and in the Medicare and Medicaid populations.

Limitations within this analysis stem from the dataset and statistical methods used to examine research questions. While the IBM Watson MarketScan® Databases include data from a variety of employers and health plans, the analysis is ultimately not generalizable to trends in Medicare, Medicaid, cash-paid services or healthcare systems outside of the U.S. In the databases, patient data is recorded at the site of care. As data were aggregated at the state level, a key assumption was made that patients receive treatment with filgrastim in the same state in which the primary insurance holder resides. The influence of manufacturers' control of the biologics market may differ by state and impact use of biosimilar products. As this factor is not captured in IBM Watson MarketScan ® Databases, it will remain a limitation of the analysis as a potential omitted variable. Furthermore, our average payment model is descriptive in nature, due to the varying trends in average biologic payment growth prior to the introduction of biosimilars. Evidence has suggested that biosimilar uptake varies by therapeutic area, therefore limiting the generalizability of these results.

Previous models have estimated large savings in the U.S. overall with $3.3 billion in 2016 due to biosimilars and approximately $54 billion between 2017 and 2026 in direct biologic costs[1]. However, trends in state-level biosimilar use and cost savings have yet to be examined and exploring sub-national differences in biosimilar use that are play an important role in the realization of the cost benefit of biosimilars. The results of this analysis add to the growing body of knowledge on the impact of biosimilar introduction in the U.S. and highlight the importance of heterogeneous trends at the state-level. Not all states operate similarly when it comes to biosimilar filgrastim use and exploring what makes some states high adopters could be the key to achieving the goal of lowering biologic costs by increasing the use of biosimilars. By identifying three unique groups of states, we present potential pathways healthcare systems and payers to increase utilization in states with lower use of biosimilar filgrastim. Not all states operate similarly when it comes to biosimilar filgrastim use, and exploring what makes some states high adopters could be the key to achieving the goal of biosimilars.

Chapter 2. BIOSIMILAR SUBSTITUTION LAWS ANALYSIS

2.1 INTRODUCTION

The United States developed an abbreviated approval pathway through the Biologics Price Competition and Innovation Act of 2009 (BPCIA) for products that are highly similar to an FDA-approved reference biologic[1]. The first designated biosimilar to reach the U.S. market was filgrastim in 2015, a biologic with a primary indication to reduce febrile neutropenia in cancer patients receiving myelosuppressive anti-cancer treatment[2,3]. After FDA approval, uptake of a biosimilar can be impacted by several factors. States can influence the uptake of the products through legislation at the state level. In addition to state laws on biosimilar use, additional factors may impact product use such as disease epidemiology for biosimilar-related indications and varying payer practices for biosimilar coverage and reimbursement[4–8].

For decades, states have played an important role in the regulation of reference and non-reference (i.e. generic or biosimilar) prescription drugs. When generic drug alternatives for small molecule drugs were gaining market share in the U.S., starting in the 1980s, several researchers reported that state-level generic drug substitution legislation impacted generic use[9,10]. Recent studies have further noted that differential content in state-level generic drug substitution legislation (e.g. whether or not a state has mandatory generic substitution in place) leads to different effects on generic drug use[11]. Anticipating the forthcoming availability of biosimilar alternatives to reference biologics as well as the complexity of approving biosimilars relative to generics for small molecule drugs, states began processes to amend or propose state laws to address unique aspects of biosimilars[5]. Amid fears that generic substitution laws may be misapplied to biologics products that are not identical, states began to propose and pass biosimilar laws beginning in 2013.

In this analysis, we aim to understand if the presence of state-level biosimilar substitution laws is associated with a state's uptake of biosimilar filgrastim. First, we examined the content and timing of state-level biosimilar substitution laws, including the details of their specific components. Next, we used healthcare claims data to quantify the use of biosimilar filgrastim at the state level and conducted an analysis to determine if the presence of biosimilar substitution laws was associated with higher utilization of biosimilars. The results from this analysis provide dual insight into the decentralized use of biosimilar filgrastim in the U.S. and the potential role of legislation in encouraging or inhibiting use of the product at a decentralized, state level. As more biosimilar products become available with potential impacts on access and healthcare expenditures, it is critical to understand the factors associated with uptake. This study examines the role of state laws as a potential tool to impact uptake of biosimilars and help to reach their potential of lowering biologic payments in the U.S.

2.2 METHODS

In this analysis, we considered how the presence or absence of a biosimilar substitution law at the time of biosimilar filgrastim market entry, and its specific components, are associated with states' biosimilar uptake classification through a latent class analysis. The primary covariate of interest is modeled in two different ways: 1) the status, i.e. presence or absence of one or more state laws on biosimilar substitution (binary) and 2) the content of the biosimilar legislation (binary variables). Using data from National Conference of State Legislatures (NCSL) and specific state legislature website files[20] we determined if a state-level legislation had been signed into law by the time of filgrastim biosimilar market availability (FDA approval March 2015; market availability September 2015). While the content of signed biosimilar substitution laws may differ by state, they can notably be assessed on the presence or absence of five specific characteristics[9]:

1. “Dispense as Written” option: Whether or not the prescriber would be able to prevent substitution by stating “dispense as written” or “brand medically necessary” on a biologic prescription
2. Prescriber notification: Some legislation requires “notification” to a prescriber of possible substitution while others allow for a more passive communication (i.e. electronic communication on ultimate product dispensed in an information system which can be later accessed by prescriber)
3. Patient notification: Whether or not a patient must be notified of the substitution or any information regarding the cost of the biologic and biosimilar
4. Records: whether prescribers or pharmacists are required to keep records of substituted biologics
5. State database: whether or not a state must keep a public list of available biosimilar options.

Using the same data sources, one researcher from the study team indicated if the biosimilar law contained any of five sub-components: dispense as written, prescriber notification, patient notification, records of substituted biologics, and state database. The researcher-determined classification of the presence or absence of these components were checked with the NCSL databases, and no incongruent classifications were identified.

Using the IBM Watson MarketScan® Databases, data were abstracted from 2010-2017 for each medical benefit claim of filgrastim (Neupogen®), tbo-filgrastim (Granix®), filgrastim-sndz (Zarxio®), and peg-filgrastim (Neulasta ®) administered during both outpatient and inpatient services. [12] Utilization of biosimilars was measured as a use ratio, with total patients receiving biosimilar filgrastim (filgrastim-sndz) as a numerator and the total number of patients who use any filgrastim-containing product as a denominator in each month and state. In the overall dataset, patients with missing enrollment identification numbers were excluded (4.9% of patients) along with biologic claims that did not have any associated cost (<1 of biologic claims). Lastly, in the final analysis, states with low sample sizes (<10 claims) for at least 50% of the months in the study timeline were excluded, which lead to the exclusion of one state (Hawaii).

Exploratory analysis of the derived outcome measure suggested a strong degree of heterogeneity in biosimilar uptake between states. Due to such heterogeneity, modeling the impact of biosimilar substitution law directly on an average uptake trend would exclude potentially meaningful information present in distinct subgroups of states within the data. In order to identify if such subgroups were present, a subject-centered latent class approach was used where states served as subjects for the analysis. For longitudinal data, latent class modeling is an approach which considers the trend, or growth, of an observed variable for study subjects over time and can identify unique groups based on the trend of subjects' time-varying outcome measure[16–18]. Using latent class mixed modeling (LCMM) a latent class model was performed on the outcome variables of use ratio as previously defined. From the analysis, subjects (states) are classified into a specified number of latent classes based on their outcome of biosimilar use. Model fit was assessed by

Bayesian Information Criteria (BIC) and log-likelihood and the model with the strongest fit that retained at least 10% of the subjects in each class was selected.

A multinomial logistic model was used to estimate the log odds of a state's membership in an indicated latent class relative to a reference class. This model was chosen due to having more than two identified latent classes among states based on biosimilar adoption. Additionally, despite the ordinal nature of our outcome variable (latent class defined by low, medium, and high biosimilar use), the data did not support the assumption of proportional odds (Chi squared test yielded $p<0.05$) and an ordinal logit model was not utilized to allow for differences in relationships between covariates and state classes.

In addition to utilization measures, covariates were identified to adjust for observable changes over time in the study population that can influence biosimilar uptake. These covariates are defined in Table 2.4 below [13–15]. As a policy covariate, we included a binary variable to account for generic substitution laws that were not displaced in states with the passing of biosimilar substitution and could impact the association product uptake.

Table 2.1. Analysis variable summary

Table 2.1. Analysis variable summary

Variable	Long Description	Method for inclusion in model
Outcome: State biosimilar utilization group	Identified utilization group from LMM	Categorical variable noting state membership classification from latent model.
Primary covariates. Status of state legislation on biosimilar	Status of states' legislation on biosimilars at the time of biosimilar market entry.	Binary including if law was present and five additional binary variables for each component of biosimilar laws.
Time period	Monthly time period	Monthly time period

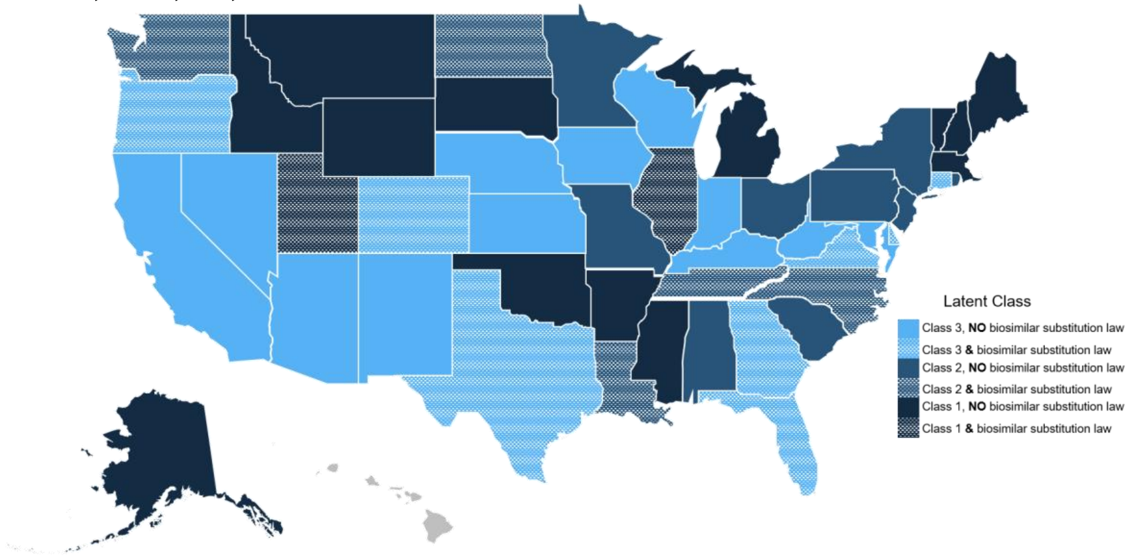
Population size	Eligible population	Log of total eligible patient population for each state and month
Second generation product utilization	Use of peg-filgrastim	Percentage of total fills that are second generation product (peg-filgrastim)
Biologic utilization	Use of all four biologics	Log of total products fills (cumulative for all four noted biologic products) for each state and month
Comorbidities	Health state of the eligible patient population	Proportion of patients with a comorbidity index of 0, from Elixhauser co-morbidity index scores (based on ICD-9 and ICD-10 codes from IBM Watson MarketScan® Databases) for eligible patient population at in each state and month.
Payer type	Indication of payer market in each state	Percentage of eligible population covered by PPO for each state and time period
Age	Age of patient	Average age of males and average age of females for eligible patients for each state and month
Gender	Gender of patient	Percentage of patients that are male in each state and month

2.3 RESULTS

Among the 50 states in the U.S., 42 have signed biosimilar substitution laws and 15 (~36%) had such laws in place when biosimilar filgrastim was first available on the market. Overall, we found that 8 states had laws which included the need to notify physicians when a biosimilar substitution was made, 15 require that a patient is notified at the time of their biosimilar substitution, 14 allow for a biosimilar substitution to be blocked when noted in a clinician's prescription, 12 require that pharmacies keep a record of all biosimilar substitutions that are made, and 9 require that a list of potential biosimilar substitutes are kept updated throughout the state.

For the latent class analysis and covariate data collection, 1,454,579 claims of one of the four noted filgrastim-containing biologics products were identified. Claims with missing data on enrollee identification and payment were excluded from the analysis, resulting in 1,383,742 claims in the final dataset. Based on model fit assessments, a model with three latent class was selected: Class 3 (highest biosimilar use), Class 2 (middle biosimilar use), Class 1 (lowest biosimilar use). A summary of states' latent class designation (Class 3 highest biosimilar use, Class 2 medium biosimilar use, and Class 1 lowest biosimilar use) is provided in Figure 1 below. The presence of biosimilar substitution laws at the time of marketing for biosimilar filgrastim is also depicted in Figure 2.1. While 42 states have enacted a biosimilar substitution law to date, only 15 states had such a law enacted by September 2015.

Class 3 (highest biosimilar use)	**Class 2**	**Class 1 (lowest biosimilar use)**
States (n): 20* States (%): 40.82% PP: 0.8871 AZ, CA, CO+, CT+, DE+, FL+, GA+, IA, IN, KS, KY, MD, NE, NM, NV, OR+, TX+, VA+, WI, WV	States (n): 14* States (%): 28.57% PP 0.7533 AL, LA+, MN, MO, NC+, ND+, NJ, NY, OH, PA, RI, SC, TN+, WA+	States (n): 15* States (%): 30.62% PP: 0.8952 AK, AR, ID, IL+, MA, ME, MI, MS, MT, NH, OK, SD, UT+, VT, WY



PP: Posterior probability for states belonging to each class
*Data for Hawaii were dropped due to a small sample size, + state had an approved biosimilar substitution law in place by September 2015, the time that biosimilar filgrastim was approved.

Figure 2.1 Average smoothed uptake trends of biosimilar filgrastim by latent class

Two multinomial logistic models were analyzed. In the first, we look at the aggregate association of the presence of a biosimilar law (indicated in a single binary variable) on the log odds that a state was designated into either Latent Class 3 (High Use) or 2 (Medium Use) relative to Latent Class 1 (Low Use). Results from the first model are noted in Table 2.5 below. We see a non-significant association between the presence of a biosimilar substitution law on the odds that a state belongs in the Medium Use class relative to the Low Use class (p=0.185) and that a state belongs to the High Use class relative to the Low Use class (p=0.124). Among covariates, we find a significant association with population health, suggesting that states with less healthy populations (those with higher proportion of patients with an Elixhauser score of 5+) have a significantly lower odds of belonging to the Medium Use class relative to the Low Use class.

Table 2.2. Multinomial logistic model regression results for aggregated biosimilar substitution law

Table 2.2. Multinomial logistic model regression results for aggregated biosimilar substitution law

Variable	Value	SE	p-value
Latent Class 2 (reference Latent Class 1)			
(Intercept)	-4.540	1.294	0.074
Biosimilar substitution law	0.467	0.351	0.185
Automatic generic sub. law	0.859	0.510	0.092*
Age (males)	0.003	0.012	0.835
Age (females)	-0.041	0.016	0.445
Male	0.989	0.610	0.105+
Log(Population)	0.275	0.143	0.054
% patients covered by PPO	0.633	0.385	0.100+
Elixhauser score 0	0.383	0.435	0.385
Elixhauser score 1	0.369	0.365	0.317
Elixhauser score 2	0.433	0.226	0.055*
Elixhauser score 3	-0.906	0.266	0.091*
Elixhauser score 4	0.774	0.476	0.104
Elixhauser score 5+	-0.593	0.122	0.002***
% of biologic claims 2^{nd} Gen.	-0.004	0.001	0.072*
Latent Class 3 (reference Latent Class 1)			
(Intercept)	-2.683	0.665	0.021
Biosimilar substitution law	0.395	0.257	0.124
Automatic generic sub. law	0.702	0.401	0.079*
Age (males)	0.002	0.008	0.841
Age (females)	-0.006	0.013	0.281
Male	-0.492	0.445	0.329
Log(Population)	0.473	0.144	0.001**
% patients covered by PPO	0.171	0.216	0.435
Elixhauser score 0	0.183	0.093	0.049**
Elixhauser score 1	1.039	0.888	0.245
Elixhauser score 2	1.966	1.257	0.118
Elixhauser score 3	0.457	0.673	0.508
Elixhauser score 4	-0.642	0.365	0.976

Elixhauser score 5+	-0.685	0.374	0.919
% of biologic claims 2nd Gen.	0.001	0.005	0.795

A second model included five binary variables to indicate the presence or absence of the previously noted components of biosimilar substitution laws. In this model, we see a notable positive association between requirement that states maintain a listing of biosimilar substitutes and the odds of belonging to the Medium Use class vs. Low Use class (~58% increase, p=0.084) and a significant positive association when considering membership to the High Use class vs. Low Use class (~50% increase, p<0.05). The ability to block a biosimilar substitute via notation on a prescription had a notable negative impact on the odds of being in the High Use class vs. the Low Use class (~46% reduction, p=.107). Additional covariates that are associated with use designation in Medium Class states include the presence of a generic law that allows for automatic substitution (positive association), increase coverage by PPO (positive association), and high level of comorbidities (negative association). Sensitivity analysis conducted for only the Medium Use Class and High Use Class, demonstrate instability in payment findings and the dependency of the results on the reference class that is chosen.

Table 2.3. Multinomial logistic model regression results for biosimilar substitution law sub-components

Table 2.3. Multinomial logistic model regression results for biosimilar substitution law sub-components

Variable	**Value**	**SE**	**p-value**
Latent Class 2 (reference Latent Class 1)			
(Intercept)	-7.827	2.433	0.135
Physician notification	0.822	0.551	0.136
Patient notification	0.610	0.497	0.221
Substitute can be blocked	-0.934	0.503	0.901
Record of biosimilar required	-0.431	0.251	.806
List of biosimilar maintained	0.460	0.267	0.084*

Automatic generic sub. law	0.527	0.168	0.002***
Age (males)	-0.027	0.014	0.910
Age (females)	-0.009	0.005	0.917
Male	0.649	0.665	0.334
Log(Population)	0.162	0.100	0.105+
% patients covered by PPO	0.989	0.487	0.042**
Elixhauser score 0	-0.985	0.526	0.890
Elixhauser score 1	-0.299	0.139	0.686
Elixhauser score 2	-0.360	0.206	0.981
Elixhauser score 3	-0.283	0.158	0.949
Elixhauser score 4	0.752	0.694	0.282
Elixhauser score 5+	-0.717	0.162	0.007***
% of biologic claims 2nd Gen.	-0.006	0.002	0.100
Latent Class 3 (reference Latent Class 1)			
(Intercept)	-1.668	0.842	0.809
Physician notification	0.302	0.174	0.081*
Patient notification	0.659	0.483	0.173
Substitute can be blocked	-0.610	0.175	0.107+
Record of biosimilar required	-0.056	0.034	.755
List of biosimilar maintained	0.404	0.128	0.002***
Automatic generic sub. law	-0.292	0.167	0.978
Age (males)	-0.007	0.003	0.329
Age (females)	-0.002	0.001	0.596
Male	-0.612	0.297	0.750
Log(Population)	0.521	0.291	0.073*
% patients covered by PPO	-0.171	0.094	0.934
Elixhauser score 0	0.922	0.502	0.066*
Elixhauser score 1	-0.415	0.237	0.978
Elixhauser score 2	-0.109	0.055	0.797
Elixhauser score 3	0.717	0.821	0.390
Elixhauser score 4	0.558	0.808	0.500
Elixhauser score 5+	-0.340	0.109	0.167
% of biologic claims 2nd Gen.	-0.001	0.001	0.548

2.4 DISCUSSION

With a growing number of approved biosimilars in the United States and an increased number of biosimilar products in development, we stand capable of achieving cost-reduction in drug expenditures with the availability of a biologic substitution. In order to achieve the cost-savings potential of biosimilars, utilization of the filgrastim containing products must shift from branded to biosimilar and this shift can be facilitated or hindered by different policy levers including laws. In this study, we examined the association of one type of law--biosimilar substitution—on the uptake of biosimilar filgrastim across states. This exploration lends insight into if and to what extent these laws and their specific components may either encourage or inhibit high biosimilar use.

Although an aggregate impact of biosimilar substitution laws assessed as a single variable was not observed, varying results were seen when we examined the components of such laws individually. The lack of a significant association seen between the overall presence of a biosimilar substitution law and biosimilar uptake may be related to the mixed directions of such an association. Some state's laws may encourage biosimilar use while some inhibit biosimilar adoption, and others may include both encouraging and inhibiting components in one law.

When examining the components of each law, we found that maintaining lists of available biosimilar substitutes at the state level was positively associated with biosimilar uptake. This finding suggests that the information in such lists potentially encourages clinicians and pharmacists to search for and prescribe biosimilar filgrastim, driving up utilization. In addition, signals indicated that the presence of a law that allows for a biosimilar substitute to be blocked through notation in a prescription could be negatively associated with biosimilar use in some states. Such a result could indicate a direct impact of substitution blocks on biosimilar uptake and/or could be signals of a climate that is cautious on biosimilar uptake. Patient notification may be associated with higher biosimilar uptake, indicating that patient information may help in understanding the efficacy and risks of biosimilars, encouraging an informed choice for their use.

Among additional factors beyond policy that impact biosimilar use, we note that higher levels of unhealthy patients within a state may be related to lower biosimilar use. In these cases, clinicians may be hesitant to prescribe a biosimilar or switch products with patients who are very sick and would be most vulnerable to the product with less clinical and real-world evidence. Larger population is associated with higher biosimilar use in some states, indicating that cost-cutting measures may be carried out most strongly in states that could reap the greatest absolute benefit.

As policy makers strive to place optimal levers to ensure the safety of biosimilars without limiting their appropriate use, the findings from this study can provide initial guidance. First, we see that maintaining a state-level list of available biosimilar substitutes may help in biosimilar uptake, presumably by providing easy access to information on alternative biologic option. Next, we observe a negative association with the ability of prescriber to note “prescribe as written” and block a prescription for a biosimilar and the uptake of biosimilars. The direction of this association is ambiguous—either this component of the laws impacts biosimilar uptake or a negative uptake environment has lead to both low uptake of biosimilars and law that include biosimilar substitution blocking. Further research can aim to explore the directionality of the associations seen in this analysis, include additional covariates reflecting industry actions, and determine if such associations expand to other product areas outside of filgrastim and poplulations in Medicare and Medicaid.

Limitations within this analysis stem from the dataset and statistical methods used to examine research questions. The IBM Watson MarketScan® Databases are ultimately not generalizable to trends in Medicare, Medicaid, cash-paid services or healthcare systems outside of the U.S. Additionally, while the database is robust, it cannot capture aspects such industry responses to biosimilar entry which may lead to bias in the analysis. In analyzing the components of state biosimilar substitution laws, we used a simplifying codification (i.e. classification into five binary variables) that may not capture the full nuisance and application of laws. Triangulation of researcher-assigned classification with the NSLC helped to validate our assessments of state laws. Additionally, the use of biosimilar law status at a single time point was used in the multinomial logit regression, which was determined to be an acceptable simplifying assumption in the context of this study but is nonetheless a limitation in that it captures a time period at which 30% of all states had a biosimilar substitution law. This assumption could potentially bias our analysis toward the null hypothesis that biosimilar substitutions laws had no significant association on biosimilar uptake.

The key findings of this study demonstrate that the mere presence or absence of a biosimilar substitution law may not be as important as the specific components contained within each of those laws, when applied with the goal of increasing biosimilar use. A balanced use of policy levers is needed to ensure safety and uptake of the new products that arrived in the U.S. marketplace four years ago. While specific types of biosimilar substitution laws, such as allowing for a prescriber to block a substitution, may be related to a decrease in biosimilar use, others like keeping lists of available biosimilar substitutes and patient notification may help to increase the product's uptake and bring us closer to achieving related healthcare cost savings.

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