FEATURE ARTICLE

Naming Convention, Interchangeability, and Patient Interest in Biosimilars

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Although biosimilars may offer cost savings over their comparable biologics, use of biosimilars in the United States remains relatively low. This study investigates two barriers to uptake of biosimilars in the United States. First, the U.S. Food and Drug Administration requires that four-letter suffixes be added to the nonproprietary names of all biosimilars, as well as to the nonproprietary names of all biologics approved after March 2020. Second, biosimilars are not interchangeable with their reference biologic product at the pharmacy counter; a new prescription is needed for the biosimilar to be dispensed in place of the biologic. We conducted two behavioral experiments to examine the effects of the naming convention and interchangeability designation on patients' interest in biosimilars. We found that, absent the mention of needing a new prescription, adding four-letter suffixes to biosimilars' nonproprietary names decreased participants' likelihood of using the biosimilars. When participants were told whether a biosimilar required a new prescription, they were more interested in the biosimilar when it did not require a new prescription, and this effect was driven by participants' perceived similarity of the biosimilar to the biologic. The effect of interchangeability dominated the suffix effect. Our results suggest that both biosimilar suffixes and interchangeability issues provide signals to patients regarding the perceived similarity of biosimilars to their reference biologics and influence patient usage of biosimilars.

Biosimilars can benefit patients by offering more therapeutic choices and potential cost savings. Limited patient interest in biosimilars, however, is constraining biosimilar uptake in the United States (1). Surveys suggest that >80% of patients taking biologics prefer not to switch to a biosimilar and are concerned about biosimilars' efficacy and safety (2). Two factors that could potentially influence patients' interest in biosimilars are nonproprietary naming conventions and drug interchangeability (1).

Biologic and biosimilar drugs have proprietary and nonproprietary names. The proprietary name is the trademarked brand name of the drug that only the drug maker can use. The nonproprietary name is the proper, or scientific, name of the drug, indicating its composition, which is not trademarked and can be used by multiple branded drugs (3). The U.S. Food and Drug Administration (FDA) requires that a four-letter suffix that is devoid of meaning be added to the nonproprietary names of all biosimilars, as well as to the nonproprietary names of all new biologics to be approved as of March 2020 (4). This naming convention further distinguishes between biologics and biosimilars, which otherwise would have the same nonproprietary name given their similar composition. Some concerns have been raised that the naming convention might reduce patients' interest in biosimilars and limit biosimilar uptake (5).

The requirements for biosimilar licensure, established by the Biologics Price Competition and Innovation Act of 2010, are more rigorous than those for small-molecule generic products. Approval of biosimilars is not only based on chemical similarity, like small-molecule generics, but also on clinical studies involving affected patient populations. In addition to demonstrating similar chemical structure and bioavailability compared with the reference product (the standard requirements for approval of small-molecule generics), biosimilars must also demonstrate that they are similar to the reference product in terms of pharmacokinetics, efficacy, safety, and immunogenicity (6,7). Furthermore, unlike with small-molecule generics, for which FDA approval also automatically allows pharmacists to substitute a generic for its reference product without a new

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TABLE 1 U.S. Regulatory Approval Requirements for Biosimilars: Comparison With U.S. Requirements for Small-Molecule Generics and to E.U. Requirements for Biosimilars

Drug type	Biosimilars	Small molecule generics	Biosimilars
Setting	United States	United States	European Union
Regulatory agency[1]	FDA	FDA	EMA
Approval pathway regulation	Biologics Price Competition and Innovation Act of 2010	Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)	Directive 2004/27/EC of 2004
Approval requirements[2]	• Analytical (in vitro) studies: demonstrate "highly similar" chemical composition, purity, and quality to the reference product • Toxicity studies on animal model • Comparative clinical studies on patients with the clinical condition: demonstrate safety and effectiveness, assess immunogenicity, elucidate pharmacokinetics and pharmacodynamics	• Bioequivalence studies: demonstrate same chemical composition, purity, and quality as the reference product and same bioavailability in healthy volunteers	• In vitro assays and impurity profiling • Comparative clinical studies on patients with the clinical condition: demonstrate safety and effectiveness, assess immunogenicity, and elucidate pharmacokinetics and pharmacodynamics • Post-approval pharmacovigilance/ monitoring studies
Criteria for granting interchangeability[3] (defined as allowing for the drug to be substitutable for the reference product by a pharmacist without the intervention of the prescriber)	• Fulfillment of all criteria for biosimilarity • Clinical "switching" studies: demonstrate same clinical result in any given patient and demonstrate that risk from switching is not greater than from using the reference product alone	Automatically granted upon fulfillment of bioequivalence criteria described above	• Fulfillment of all criteria for biosimilarity • Additional studies not required • Decisions made at the country level
Nonproprietary naming of product[4]	USAN-designated proper name of the biologic plus a four-letter suffix devoid of meaning	Same USAN-designated proper name as the reference drug	Same proper name as the biologic as designated by the INN convention[5]
Number of Approved Biosimilar Products as of December 2019[6]	26	NA	69

[1]The EMA was the first regulatory agency to establish a pathway for biosimilar approval. [2]The specific requirements for biosimilar approval may vary on a case-by-case basis for both the FDA and the EMA. [3]The FDA has recently modified the criteria for interchangeability for the specific case of insulins, such that proof of biosimilarity will be sufficient for granting interchangeability. [4]The nonproprietary names of all reference biologics approved by the FDA as of March 2020 will also contain a four-letter suffix devoid of meaning, which is different than the suffix of their biosimilars. [5]The INN is defined by the World Health Organization and typically adopts the same name as the USAN-designated name. [6]As of December 2019, the FDA had not approved any interchangeable biosimilar products. INN, International Nonproprietary Names; USAN, United States Adopted Names Council.

prescription, FDA approval of biosimilars does not automatically allow for interchangeability at the pharmacy. To obtain interchangeability, biosimilars must undergo additional "switching" studies demonstrating that alternating between the biosimilar and the reference product poses no additional risk than continuing on the reference product alone (8,9).

The FDA's regulatory requirements for approval of biosimilars are generally comparable to those of the European Medicines Agency, the first agency to have established a biosimilar approval pathway and the agency with the most approvals to date (9–12). However, the United States is the only country in which a four-letter suffix must be added to nonproprietary names of biosimilars and biologics (3,4,11) and the only country in which biosimilarity and interchangeability have different regulatory requirements (8,12). Table 1 compares the U.S. regulatory requirements for biosimilars to U.S. requirements for small-molecule generics and to regulatory requirements for biosimilars in the European Union.

Research Design and Methods

In this study, we conducted two behavioral experiments to examine the effects of the nonproprietary naming convention and drug interchangeability on patients' interest in biosimilars. Both experiments received institutional review board approval from Clemson University, and all participants provided implied consent by participating.

Participants

Participants were recruited using Amazon's Mechanical Turk, an online marketplace that has been used extensively in behavioral experiments to understand patients' interest in prescription drugs (13). To participate, individuals must be located in the United States, have a Mechanical Turk approval rating of at least 98%, have completed at least 1,000 previous tasks on Mechanical Turk, and have passed two attention check questions. Participants received $0.50 as compensation and took an average of 5 minutes to complete the task, yielding an hourly rate of $6.00, which exceeds the estimated reservation wage of Mechanical Turk participants (14).

Experimental Design

In both experiments, participants were instructed to assume that they had type 2 diabetes that was well controlled with a fictitious prescription drug named "Karlanza (insulin glargine)." Participants were then randomly assigned to view one of several different print advertisements for a fictitious biosimilar named "Wilkisar (insulin glargine)," after which they responded to a series of questions.

In the first experiment, the print advertisement varied on two dimensions: biosimilar suffix (present or absent) and interchangeability (interchangeable or not interchangeable), composing the first four conditions. Biosimilar suffix was varied by changing the nonproprietary name of the biosimilar presented to participants: "insulin glargine-acxf" versus "insulin glargine." Interchangeability was varied by changing a phrase in the advertisement indicating that the drug "does not require a new prescription" or that the drug "requires a new prescription" for those already taking the biologic. In a fifth experimental condition, the advertisement also included a four-letter suffix in the name of the biologic product. This advertisement had a different suffix in the name of the biosimilar and indicated that the biosimilar required a new prescription (i.e., not interchangeable). Thus, participants in the first experiment were randomly assigned to one of five conditions: *1*) suffix absent, interchangeable; *2*) suffix present for biosimilar, interchangeable; *3*) suffix absent, not interchangeable; *4*) suffix present for biosimilar, not interchangeable; or *5*) suffix present for both biosimilar and biologic, not interchangeable.

The second experiment was identical to the first except that the advertisements varied the biosimilar suffix only (present or absent) and made no mention of whether the drug required a new prescription. Thus, participants in the second experiment saw one of two conditions: *6*) suffix absent, no mention of interchangeability, or *7*) suffix present, no mention of interchangeability.

All advertisements stated that the biosimilar "Wilkisar" was "highly similar to Karlanza, with no clinically meaningful differences in terms of efficacy, safety, and purity," the language frequently used in biosimilar marketing materials. All advertisements also mentioned that participants could save up to 15–20% by taking the biosimilar (1).

Measurement

After viewing the advertisement, participants responded to questions measuring their likelihood of taking the advertised drug, asking their doctor about the drug, asking their insurance company about the drug, and researching the drug online (all questions are available in Supplemental Materials). Participants were also asked about perceptions of the effectiveness and similarity of the biosimilar compared with the biologic. All questions were measured on a seven-point Likert scale, ranging from "extremely unlikely" (or "extremely ineffective") to "extremely likely" (or "extremely effective"), with the exception of perceived similarity, which was measured on a five-point Likert scale ranging from "not similar at all" to "extremely similar" to improve survey attention by varying response scales (15). To test the overall trend in participants' responses, principal component analysis was used to construct a measure of overall interest using the four questions assessing likelihood. The four variables loaded onto a single factor with an eigenvalue of 3.02, which captured 75% of the overall response variance.

Analysis

Because of the nonparametric (Likert scale) nature of the responses, differences in the ratings across conditions were tested using two-tailed Wilcoxon rank-sum tests. Our analyses combined and compared across conditions, according to the characteristics manipulated in the advertisements. First, we tested for an effect of having a suffix in the nonproprietary name of the biosimilar by comparing the conditions with and without a biosimilar suffix that did not mention interchangeability (group 6 vs. group 7). Second, we tested for an effect of having a suffix when individuals know whether the drug is interchangeable by comparing the two conditions without a biosimilar suffix to the two conditions with a biosimilar suffix (groups 2 and 4 vs. groups 1 and 3). Third, we tested for an effect of interchangeability by comparing the two conditions in which the biosimilar was interchangeable to the two conditions in which it was not interchangeable (groups 1 and 2 vs. groups 3 and 4). Fourth, we tested for an additive effect of having a

suffix on the name of the biosimilar and on the name of the biologic by comparing the condition with a suffix on both the biosimilar and the biologic to the condition where there was a suffix on the biosimilar but not on the biologic (group 5 vs. group 4; in both conditions, the drugs were not interchangeable). Finally, we implement mediation analyses to test whether participants' responses were influenced by their perceptions about the biosimilar's effectiveness and similarity to the biologic. This analysis was performed using the distribution of the product method with 5,000 bootstrap iterations (16).

Results

A total of 1,306 individuals, representing a wide range of ages, incomes, insurance types, and health, participated in the studies (Table 2). Fifty-four percent of the participants were female, 71% were <45 years of age, 27% had a chronic condition, and 4% had type 2 diabetes.

As shown in Table 3, when no mention was made regarding interchangeability, the presence of a suffix reduced the likelihood of using the biosimilar (mean 5.02, SD 1.40) compared with when the suffix was absent (mean 5.37, SD 1.31) ($P = 0.02$). When the advertisement stated whether the drug was interchangeable, the likelihood of using the biosimilar did not differ with the presence of a biosimilar suffix (mean 5.22, SD 1.48, vs. mean 5.34, SD 1.48; $P = 0.23$). However, participants' perceived similarity of the biosimilar to the biologic was lower when a suffix was present (mean 4.11, SD 0.88) than when it was absent (mean 4.22, SD 0.86) ($P = 0.04$).

When the biosimilar was interchangeable (vs. not interchangeable), participants were significantly more likely to use the biosimilar (mean 5.44, SD 1.37, vs. mean 5.11, SD 1.58; $P = 0.005$), ask their doctor about the biosimilar (mean 6.14, SD 1.20, vs. mean 5.85, SD 1.48; $P = 0.007$), and research the biosimilar online (mean 6.36, SD 1.10, vs. mean 6.10, SD 1.41; $P = 0.03$). Overall interest in the biosimilar was also significantly higher when the biosimilar was interchangeable than when it was not (mean 0.19, SD 1.61, vs. mean −0.20, SD 1.95; $P = 0.009$). Interchangeability also increased participants' perception of the biosimilar's similarity to the biologic (mean 4.22, SD 0.87, vs. mean 4.11, SD 0.86; $P = 0.03$). No effect of including a suffix on both the biologic and the biosimilar was detected when compared with including a suffix on the biosimilar only.

The mediation analyses suggested that the positive effect of interchangeability on overall interest in the biosimilar was partially explained by an increase in participants' perceptions of similarity of the biosimilar to the biologic ($z = 2.00$, $P = 0.054$).

TABLE 2 Characteristics of 1,306 Study Participants

Characteristic	*n* (%)	Characteristic	*n* (%)
Age, years		Education level, continued	
18–25	133 (10)	Associate's degree	167 (13)
26–34	451 (35)	Bachelor's degree	472 (36)
35–44	342 (26)	Some postgraduate	38 (3)
45–54	193 (15)	Master's degree	139 (11)
55–64	139 (11)	Doctor's degree	35 (3)
65–74	42 (3)	Has health insurance	
75–84	6 (<1)	Yes	1,085 (83)
Sex		No	221 (17)
Male	606 (46)	Has high-deductible health plan[1]	
Female	700 (54)	Yes	259 (20)
Household income, $		No	1,047 (80)
<25,000	244 (19)	Has prescription drug coverage[2]	
25,000–34,999	161 (12)	Yes	997 (76)
35,000–49,999	219 (17)	No	319 (24)
50,000–74,999	325 (25)	History of type 2 diabetes	
75,000–99,999	166 (13)	Yes	44 (4)
100,000–149,999	124 (9)	No	1,262 (96)
150,000–199,999	45 (3)	History of other chronic condition	
200,000–249,999	5 (<1)	Yes	354 (27)
≥250,000	17 (1)	No	952 (73)
Education level		Use of prescription drugs	
Some high school	7 (<1)	Yes	528 (40)
High school	145 (11)	No	778 (60)
Some college	303 (23)		

To participate in the experiment, individuals must have been located in the United States, had a Mechanical Turk approval rating of at least 98%, have completed at least 1,000 previous tasks on Mechanical Turk, and have passed two attention check questions. From the total of 1,946 individuals who completed the experiments, we excluded 640 (33%) who failed either of two manipulation check questions. The characteristics of the individuals who failed the manipulation checks did not differ in any statistically significant ways from the characteristics of those who successfully completed these checks and comprised our final sample, with the exception that the latter were slightly older than the former (mean age 39 vs. 37 years, $P = 0.02$). Demographic characteristics were similar across both experiments. [1]Participants who indicated that they did not have health insurance or were unsure whether they had a high-deductible health plan were considered to not have a high-deductible health plan. [2]Participants who indicated that they did not have prescription drug coverage or were unsure whether they had prescription drug coverage were considered to not have prescription drug coverage.

Discussion

To our knowledge, this is the first study to examine the effect of biosimilar naming convention and interchangeability on individual behavior. We found that, absent the mention of interchangeability, adding a four-letter suffix to the nonproprietary name of biosimilars decreased participants' self-assessed likelihood of using the biosimilar. However, this relationship was dominated by the effect of interchangeability; when participants were told whether the biosimilar required a new prescription, they were

TABLE 3 Responses Among Participants Exposed to Different Naming and Interchangeability Conditions of Biosimilars on Advertisements

	Experiment 1					Experiment 2	
	Group 1: Suffix Absent, Interchangeable (n = 252)	Group 2: Suffix Present, Interchangeable (n = 203)	Group 3: Suffix Absent, Not Interchangeable (n = 223)	Group 4: Suffix Present, Not Interchangeable (n = 186)	Group 5: Suffix Present for Both Biosimilar and Biologic, Not Interchangeable (n = 193)	Group 6: Suffix Absent, No Mention of Interchangeability (n = 122)	Group 7: Suffix Present, No Mention of Interchangeability (n = 127)
Ask your doctor about the drug[1]	6.18 (1.16)	6.09 (1.24)	5.84 (1.45)	5.86 (1.52)	6.02 (1.17)	6.02 (1.35)	6.16 (1.11)
Research the drug online	6.35 (1.14)	6.37 (1.03)	6.14 (1.33)	6.05 (1.49)	6.18 (1.06)	6.27 (1.10)	6.25 (1.12)
Ask your insurer about the drug	5.56 (1.70)	5.75 (1.46)	5.52 (1.62)	5.37 (1.77)	5.56 (1.49	5.65 (1.55)	5.43 (1.64)
Use the drug	5.52 (1.39)	5.34 (1.33)	5.13 (1.56)	5.09 (1.61)	5.28 (1.28)	5.37 (1.31)	5.02 (1.40)
Overall interest[2]	0.20 (1.64)	0.17 (1.57)	−0.16 (1.89)	−0.25 (2.01)	−0.01 (1.50)	0.07 (1.77)	−0.08 (1.68)
Perceived effectiveness[3]	6.05 (0.90)	5.96 (0.94)	5.96 (1.06)	5.87 (1.05)	5.86 (1.00)	6.08 (0.75)	5.95 (0.86)
Perceived similarity[4]	4.23 (0.90)	4.20 (0.87)	4.20 (0.81)	4.01 (0.92)	4.16 (0.77)	4.28 (0.73)	4.13 (0.75)

	Rating Comparisons[5]			
	Group 7 Versus Group 6	Groups 2 and 4 Versus Groups 1 and 3	Groups 1 and 2 Versus Groups 3 and 4	Group 5 Versus Group 4
Ask your doctor about the drug	6.16 (1.11) vs. 6.02 (1.35), P = 0.75	5.98 (1.39) vs. 6.02 (1.31), P = 0.83	6.14 (1.20) vs. 5.85 (1.48), P = 0.007	6.02 (1.17) vs. 5.86 (1.52), P = 0.96
Research the drug online	6.25 (1.12) vs. 6.27 (1.10), P = 0.92	6.22 (1.28) vs. 6.25 (1.24), P = 0.86	6.36 (1.10) vs. 6.10 (1.41), P = 0.03	6.18 (1.03) vs. 6.05 (1.49), P = 0.45
Ask your insurer about the drug	5.43 (1.64) vs. 5.65 (1.55), P = 0.24	5.57 (1.63) vs. 5.54 (1.66), P = 0.94	5.65 (1.60) vs. 5.45 (1.69), P = 0.05	5.56 (1.49) vs. 5.37 (1.78), P = 0.64
Use the drug	5.02 (1.40) vs. 5.37 (1.31), P = 0.02)	5.22 (1.48) vs. 5.34 (1.48), P = 0.16	5.44 (1.37) vs. 5.11 (1.58), P = 0.005	5.28 (1.28) vs. 5.09 (1.61), P = 0.71
Overall interest	−0.08 (1.68) vs. 0.07 (1.77), P = 0.23	−0.03 (1.80) vs. 0.03 (1.77), P = 0.50	0.19 (1.61) vs. −0.20 (1.95), P = 0.009	−0.01 (1.50) vs. −0.25 (2.01), P = 0.92
Perceived effectiveness	5.95 (0.86) vs. 6.08 (0.75), P = 0.28	5.92 (0.99) vs. 6.00 (0.98), P = 0.15	6.01 (0.91) vs. 5.92 (1.06), P = 0.35	5.86 (1.00) vs. 5.87 (1.05), P = 0.77
Perceived similarity	4.13 (0.75) vs. 4.28 (0.73), P = 0.10	4.11 (0.88) vs. 4.22 (0.86), P = 0.04	4.22 (0.87) vs. 4.11 (0.86), P = 0.03	4.16 (0.77) vs. 4.01 (0.92), P = 0.17

Response rate data are mean (SD). [1]The likelihood of asking your doctor about the drug, researching the drug online, asking your insurer about the drug, and using the drug were asked in random order and measured by a Likert scale from 1 (extremely unlikely) to 7 (extremely likely). [2]Overall interest is a factor score created using principle component analysis. The four dependent variables loaded onto a single factor with an eigenvalue of 3.02, which captured 75% of the overall variance. [3]The perceived effectiveness of the drug was measured by a Likert scale from 1 (extremely ineffective) to 7 (extremely effective). [4]The perceived similarity of the drug was measured by a Likert scale from 1 (not similar at all) to 5 (extremely similar). [5]Differences in ratings across conditions were tested using two-tailed Wilcoxon rank-sum tests.

significantly more interested in the biosimilar when it was interchangeable, and the suffix effect was no longer significant. The effect of interchangeability on participants' interest was partially explained by participants' perceptions of similarity of the biosimilar to its reference drug. Taken together, both biosimilar suffix and interchangeability provide signals to patients regarding the underlying level of "true similarity" of the biosimilar to the biologic. When given interchangeability information, patients rely on that signal alone, not on the biosimilar suffix, to infer drug similarity and form an opinion about the biosimilar.

In a recent decision, the FDA has established that biosimilar insulins approved on or after March 2020 may receive interchangeability status without the need for additional "switching" studies (17). However, interchangeability is not guaranteed for noninsulin biosimilars. Furthermore, all biosimilar and biologic products approved as of March 2020 will still have a different, random four-letter suffix added to their nonproprietary names (4). Future research could examine whether the new policy translates to reducing barriers to use biosimilar insulins and whether the naming convention adds more value than complexity for patients. This research direction is important because the new policy will affect all insulin-dependent patients who could potentially benefit from increased competition provided by new biosimilar products now in the development pipeline (18), including biosimilars to insulin glargine, insulin lispro, and insulin aspart.

Limitations

This study is subject to two main limitations. First, our results focused on hypothetical patient behavior. Although some experiment participants had type 2 diabetes or other chronic conditions, the characteristics of the experiment participants did not necessarily reflect the population of individuals living with diabetes. For example, the experiment participants were relatively young and may have responded differently to suffix or interchangeability information than would older patients. Furthermore, the study required familiarity with electronic platforms, which may have selected more educated or more affluent individuals than the typical users of diabetes products. Future research could investigate how actual patients, including older adults, respond to biosimilar advertisements.

Second, the study did not investigate the behavior of providers such as prescribing physicians and pharmacists, who often rely on limited information and heuristics in making decisions. Furthermore, it is possible that educational programs provided to patients by prescribing physicians and pharmacists could affect patients' perceptions of these characteristics because patients may not understand the four-letter suffixes or the reasons for lack of interchangeability without education about these concepts. Future research could investigate whether interventions, such as providing educational programs to physicians and pharmacists or to patients, could mitigate the effects of biosimilar suffix and interchangeability identified in this study.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

All of the authors conceptualized the study, designed the instrument, interpreted the results, and drafted the manuscript for publication. J.B.G. implemented the experiments, extracted the data, and performed the statistical analysis. J.B.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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