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BRIEFLY NOTED

Cost-Saving Biosimilars’ Many Obstacles

BY HENRY I. MILLER

Innovating new drugs is an expensive and uncertain business, typically taking 10–12 years and costing, on average, \$2.55 billion to bring a new product to market. The financial risks are enormous and deserve—and require—significant financial rewards. At the same time, it’s undeniable that the costs of many new, complex drugs are high

and possibly unsustainable, both economically and politically.

In the near future, one critical, emerging pricing issue will be how rapid is the uptake of a blockbuster class of drugs called “biosimilars.” These can be thought of as generic versions of biologics, drugs that are complex biological molecules derived from living cells. Typical biologics include vaccines, allergenic products, gene therapy, and many cancer and arthritis drugs. (See “Still Awaiting the ‘Biosimilars’ Revolution,” Spring 2015.)

Generic medicines are a critical element of Americans’ health care. Since 1984, the marketing of generic versions of chemically synthesized “small-molecule” drugs—such as those used commonly to control diabetes, blood pressure, cholesterol, and pain—has been governed by legislation commonly known as the Hatch-Waxman Act. That law allows the approval of generics through an abbreviated and less costly pathway than for innovator—or brand-name—drugs, not requiring new clinical trials but only a demonstration of “bioequivalence.” That balances the need to preserve the industry’s incentive to innovate, supported by the patent system, with the benefits of competition.

The result has been a robust and hugely important generic drug industry. More than four of every five drug prescriptions are for generic drugs, which saves consum-

ers over \$200 billion annually. The price effect of newly available generic drugs is often rapid and impressive: when the first generic copy of a typical small-molecule drug reaches pharmacies, there is about a 30% drop in price, often reaching 80% as additional generic versions appear. Thus, brand-name drugs like Lipitor and Prilosec, which were economic blockbusters while their patents were intact and they had the market to themselves, have seen their market-share and revenues plummet once generics became available.

Disappointing results / When the pathway for generic drugs was established 30 years ago, biologics as a class were inconsequential compared to simpler small-molecule drugs. Today, biologics are common. Each year since 2010, they have represented the majority of new drugs that come onto the market, and they account for more than 20% of U.S. drug expenditures, with global sales topping \$150 billion annually. Last year, eight of the top 10 drugs by worldwide sales were biologics.

Hoping to replicate for biologics the success of Hatch-Waxman, in 2009 Congress passed the Biologics Price Competition and Innovation Act (BPCIA), which was supposed to begin the process of creating a generic-like pathway for biosimilars. Passage of the BPCIA was accompanied by glowing predictions of cost savings. The Congressional Budget Office estimated that biosimilars would reduce total drug expenditures by \$25 billion over 10 years.

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Steve Miller, chief medical officer of the prescription benefit plan provider Express Scripts, was far more bullish, estimating that cost savings could be a whopping \$250 billion by 2024. So far, however, those high expectations have failed to materialize.

Looking primarily through a regulatory lens, I predicted four years ago that these predictions were far too optimistic. I had several reasons for this skepticism.

First, biologics are generally made in living cells, usually bacteria, yeast, or cultured mammalian cells that have been reprogrammed to synthesize the drug by means of the insertion of new genetic material. The choice of cells and purification methods determines the nature and amount of contaminants in the final formulation. Nothing is ever 100% pure, but it's much easier to get closer to that goal with small molecules. For generic versions of small molecules, the manufacturer must only demonstrate bioequivalence, the absence of significant differences from the innovator drug in its availability at the site of its action (for example, in the blood or gastrointestinal tract). However, for biologics, various kinds of enzymatic modifications and impurities inevitably introduce variation, sometimes with unexpected results. Experience has shown that even minuscule differences in the substances that accompany—or contaminate—the active drug

substance can be clinically significant, which makes the creation of “generic” versions difficult. This is not just a biological concern, but a political one.

Second, because of these differences, regulators view biosimilars somewhat warily. The U.S. Food and Drug Adminis-

Even miniscule differences in the substances that accompany—or contaminate—the active drug substance can be clinically significant.

tration announced in 2012 “an abbreviated pathway that will depend on existing data” for biosimilars if “there are no clinically meaningful differences” from the original product. That requirement may sound innocuous, but it's a high bar to clear. It has ensured that in spite of many predictions to the contrary, this new biosimilar pathway has neither significantly changed the drug development landscape nor put a significant dent in escalating medical costs.

Understanding this failure requires some history. The FDA's involvement with biosimilars

is not new. Even before the 2012 policy was announced, regulators had approved a small number of “follow-on biologics”—biosimilars by another name. Scientific considerations dictated that all of them required a substantial amount of laboratory and clinical testing—a far more elaborate, expensive process than has been required for small-molecule generics. Despite the 2012 announcement, the FDA's approach to such products has not eased, and this is reflected in the approval numbers. The first U.S. biosimilar was

approved by the FDA in 2015 and only 18 have been approved to date. This compares with 58 by the European Medicines Agency.

Why the discrepancy? The FDA's experience with biologics, both new and follow-on varieties, is revealing. A vivid example of the potential problems with biologics occurred between 2001 and 2003, when two versions of a biologic called epoetin alfa, which treats anemia, were sufficiently different that one of them actually *caused* a 30-fold greater frequency of a severe kind of anemia. The drugs were supposed to be the same but the clinical outcomes were very different.

Cognizant of such phenomena, the FDA has long considered that even minor changes in the production of biological drugs—including the same isolation and

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purification procedures applied at significantly larger scale than previously—yield a distinct new drug that must undergo an independent demonstration of safety and efficacy. For example, some years ago the FDA reviewed a request to manufacture a biologic used to treat Pompe disease—a debilitating inherited disorder—in a new, larger-scale manufacturing facility. Although the drug was produced by the same company with the same process as at smaller scale, the FDA considered the larger-scale version to be a new product and even required that it adopt a different name; the two products were marketed as Myozyme and Lumizyme.

The head of the FDA's drug center, Janet Woodcock, has acknowledged in congressional testimony the scientific and technical challenges posed by biosimilars. She emphasized the importance of possible immunogenicity—the stimulation of an immune response (which can both inactivate the drug and cause serious side effects)—by a biosimilar drug. She noted that “the ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited,” and concluded that “some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed.” The bottom line is that clinical trials—which may need to be large in order to achieve sufficient statistical power—are generally required to demonstrate the efficacy and especially the safety of biosimilars before the FDA approves them.

A third problem for biosimilars is that various non-regulatory economic factors create disincentives to the uptake of biosimilars once they are approved. Pacific Research Institute economist Wayne Winegarden explains two of these disincentives:

One of the more important obstructions is the current “buy-and-bill” reimbursement system that disincentivizes lower-cost biosimilars. Under this system, providers purchase medicines and then, once the medicines have been administered to the patients, bill insurers for the costs of the medicine plus

their mark-up. The provider mark-up is typically a percentage of the medicine's price. Since a biosimilar's price is less than a biologic's price, providers lose money when they prescribe a lower-priced biosimilar medicine instead of a higher-priced biologic medicine. These losses are not de minimis either. A 2017 study found that in the case of one medicine class, infliximab, broad adoption of the biosimilars could decrease providers' profits by as much as \$100 million.

Next, insurance plans commonly include fail-first policies. Typically, the purpose of fail-first policies is to require patients to use lower-priced generic medicines first, then, only if the generic medicines fail to sufficiently help the patients,

Even after biosimilars are approved, their adoption rates have not been as high as predicted. Only time will tell whether they will moderate drug prices.

can a more expensive branded medicine be prescribed. As applied to biosimilars, however, fail-first policies work in reverse. In this case, the insurance clauses will only allow patients to use the less expensive biosimilars if they first failed on the more expensive biologics. Thus, as currently applied, fail-first policies bias the market against less expensive biosimilars, harming competition in the process.

A fourth problem is that patents have protected market share and the pricing power of the brand-name biologics. Most of these drugs haven't been on the market long enough for their patents to expire, at which time competitors would be permitted to launch cheaper biosimilars. It should be noted, though, that many of the initial wave of biologics are beginning to reach the end of their exclusivity period.

One final problem is that the uptake of biosimilars has been slowed by several strategies devised by the manufacturers of

the brand-name biologics in order to maintain market share. For example, originators have inhibited the sales of biosimilars by gaming the rebate system. The originators offer rebates to health insurers that agree to contracts that exclude biosimilars or, at least, provide the brand-name biologic with preferential placement on their drug formularies, which dictate how much patients pay at pharmacies. Why would insurers enter into such arrangements? Possibly because biosimilars are viewed skeptically as a result of a kind of whispering campaign to disparage them.

Although the BPCIA states explicitly that a biosimilar must be highly similar to, have the same mechanism of action as, and have no clinically meaningful differences from the reference product, that has not deterred some makers of the more

expensive brand-name products from raising theoretical concerns about the safety and efficacy of biosimilars. They claim that their goal is solely to inform and protect patients, but as H.L. Mencken

said, “When someone says, ‘It's not about money,’ it's about money.”

Conclusion / The result of all these factors is that even after the biosimilars are approved, their adoption rates are not as high as predicted. That is costly to patients and insurers. According to a study by the RAND Corporation, biosimilars are projected to be priced 10–51% below the corresponding brand-name biologic. That has not borne out.

Winegarden estimates that small-molecule generic drugs “saved the U.S. health system \$1.67 trillion between 2007 and 2016 alone.” His analysis indicates that with increasing market share of currently approved biosimilars, the savings could run well into the billions. However, at least in the short-term, the obstacles are imposing. Only time will tell whether biosimilars will become a major factor in moderating drug costs, as they should. R

The Ever-Popular Electoral College

BY PAUL E. GODEK

The electoral college is a unique and somewhat arcane institution, but its history and function are not mysterious. The electoral process is embedded in the Constitution and its structure specifies precisely how much influence each state can have on the election of the president of the United States.

Suggestions to abandon the electoral vote in favor of a national popular vote are not new and, for reasons discussed here, have never come close to implementation. Recently, however, a strategy has been devised to effectively nullify the electoral college: the so-called National Popular Vote Interstate Compact. Constitutional scholars, state lawmakers, and voters who are contemplating this strategy should understand its implications.

538 electors / First, a little history. The Constitution directs that the number of electors for each state shall equal the “Number of Senators and Representatives to which the State may be entitled in the Congress.” Every state has two senators and at least one representative, so every state has at least three electoral votes.

The number of representatives was fixed at 435 by the Apportionment Act of 1911; that number was affirmed by the Permanent Apportionment Act of 1929. The 23rd Amendment (ratified in 1961) assigns three electoral votes to the District of Columbia. Unless a new state is added to the realm or Congress revises the number of representatives—something it has not done in over 100 years—the current total of 538 electoral votes will prevail. A simple majority—270 votes—is required to win the election.

So how are the 385 additional representatives, beyond the minimum of one per

state, apportioned among the states? As specified in the Constitution, the apportionment process occurs every 10 years, based on state populations as determined by the official decennial census. The current apportionment method, in place since 1941, is credited to the mathemati-



cian Edward Huntington and to Joseph Hill, chief statistician of the U.S. Census Bureau. The Huntington–Hill method, also known as the “equal-proportions” method, applies a straightforward mathematical weighting formula to determine how many representatives each state shall have. Adoption of the Huntington–Hill method does not appear to have been controversial; it simply made formulaic the ad hoc methods that had been applied over the preceding decades.

One attribute of the electoral college’s design is apparent. The method for appor-

tioning representatives among the states, and consequently determining the number of electoral votes, ensures that small states (as measured by population) will have shares of the electoral vote that are greater than their shares of the national popular vote. Conversely, large states will have electoral vote shares that are less than their shares of the national popular vote. For example, the smallest state, Wyoming, with one congressional representative, has 0.6% of the electoral vote and 0.2% of the U.S. population. At the other end of the size distribution, California, with 53 representatives, has 10.2% of the electoral vote and 12.0% of the U.S. population.

In 2016, 32 states and the District of Columbia had an electoral vote share greater than their population share. Those states have a greater potential influence on

the electoral vote than they would have on the national popular vote. This is not a new pattern. Throughout U.S. history, the majority of states—the smaller ones—have had an electoral share greater than their population share.

Compared to a national popular vote, a small state is likely to prefer the electoral college system because of the relative advantage conferred. Any state, large or small, may well prefer the system that is not dominated by a handful of the largest states. (When considering what system a state “prefers,” I am referring to what the

PAUL E. GODEK is a senior vice president of the consulting firm Economists Incorporated. The views expressed in this article are his own. This article is an extension of his paper “Determining States’ *A Priori* Preferences for the Electoral College: 1788–2016” (*Cato Journal*, Fall 2018).

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voters of the state are likely to prefer in general, without consideration of the outcome in any particular election.) Because a majority of states are likely to prefer the electoral college, it has never been susceptible to removal by constitutional amendment, which requires the assent of not just a majority but three-fourths of the states.

Overruling state voters / Recently, however, another consideration has come into play. Several states have joined the National Popular Vote Interstate Compact (NPVIC). The NPVIC is an agreement, among the states that join, to award all of their electoral votes to the presidential candidate with the highest share of the national popular vote. The agreement goes into effect if enough states join the NPVIC to account for 270 electoral votes, the number needed to win the election. As of now, the NPVIC includes 12 states and the District of Columbia. Together, they account for 181 electoral votes.

Is the NPVIC in accordance with the Constitution? Article I, Section 10, Clause 3 declares, “No State shall, without the Consent of Congress, ... enter into any Agreement or Compact with another State.” It seems clear, therefore, that the NPVIC would require congressional approval to become operational. But, as someone once said, in law nothing is certain but the expense. Let’s put this issue aside for present purposes.

Article II, Section 1, Clause 2 of the Constitution, already quoted in part, declares, “Each State shall appoint, in such Manner as the Legislature thereof may direct, a Number of Electors, equal to the whole Number of Senators and Representatives to which the State may be entitled in the Congress.” Accordingly, it is for the states to direct how their electors will vote. Every state—except Maine and Nebraska, which split their electoral votes—has determined that all of its electors shall vote for the winner of the popular vote in the state; winner take all. The dominance of a winner-take-all allocation should not be surprising. Each state would presumably want to maximize its influence on

the election. I cannot explain Maine and Nebraska.

Since the Constitution gives each state the exclusive right to assign its electors as it sees fit, joining the NPVIC could be seen as just another way for a state to assign its electors. Let us consider, however, the possible outcomes if NPVIC membership grows to account for 270 electoral votes, so that it becomes operative.

If the winner of the national popular vote would have won the electoral vote (absent the NPVIC), then the NPVIC would not affect the outcome of the election. Nonetheless, an NPVIC state that voted for the loser of the national popular vote would have its electors assigned to the winner of the national popular vote. The majority of that state’s voters might well feel cheated, but the outcome of the election would not be affected by the state’s participation in the NPVIC.

What happens if the winner of the national popular vote would have lost the electoral vote (absent the NPVIC), as happened in the most recent election? If the winner of a state’s popular vote also wins the national popular vote, then that candidate already has the state’s electoral votes; participation in the NPVIC would not change the state’s electoral vote. But if the winner of a state’s popular vote loses the national popular vote, then that state’s electors would be shifted from the state’s popular vote winner to the national popular vote winner. That, along with the shift of other NPVIC states’ electoral votes, would change the outcome of the election. The majority of the state’s voters would definitely feel cheated.

Joining the NPVIC means that the assignment of a state’s electoral votes in a future election might not be in accord with the will of the majority of the state’s voters. That outcome is, indeed, the entire and explicit purpose of the NPVIC. If the winner of a state’s popular vote is the loser of the national popular vote, then the electors will be allocated contrary to the majority of that state’s voters. By joining the NPVIC, therefore, a state commits itself to disenfranchising its own voters in some future election.

Regardless of the legal issues that raises, why would any state join a system that is intended to allocate electors contrary to the preferences of the state’s voters? There are several possible reasons. Some of the largest states might join because they see the NPVIC as an effective repeal of the electoral college—which it is—and they prefer the national popular vote for the reasons discussed above. Some small states might join because they see the NPVIC as a way of avoiding a replay of the 2016 outcome; those would be the small states that see themselves as politically aligned with the largest states. Indeed, participation in the NPVIC so far reflects these explanations. Large states California, New York, and Illinois have joined, and all of the joining states voted for Clinton over Trump in 2016.

Nullifying the Constitution and the will of state voters / The electoral college does not correlate perfectly with the national popular vote. That is not a flaw; that is its purpose. And there is a powerful reason for the persistence of the electoral college: a majority of states prefer it, which has been the case throughout U.S. history.

If the NPVIC becomes operational, two outcomes would result. First, the only vote tabulation of consequence would be the national popular vote. The electoral college would be effectively nullified without constitutional amendment, likely by an agreement among a minority of the states. Second, NPVIC states would be enacting a system designed, under specific circumstances in a future election, to disenfranchise their own voters.

It is important to remember that the distribution of congressional representatives (and consequently of electors) was not happenstance, but rather the result of purposeful compromises among the states, in consideration of the wide variation in state populations. The Constitution and subsequent laws embody several such accommodations, so as to prevent a small number of large states from dominating political outcomes. As one of those accommodations, the electoral college has proven to be durable, so far. R

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