contemporaries reached well beyond the Civil War years and have influenced principles and practices of American medicine to the present day. These changes were scientific, procedural, and administrative in character, but perhaps most important, they marked the start of a transformation in the way doctors, patients, and the public thought about the practice of medicine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the History of Medicine Division, U.S. National Library of Medicine, National Institutes of Health, Bethesda, MD.

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DOI: 10.1056/NEJMp1502748

Progress and Hurdles for Follow-on Biologics

Ameet Sarpatwari, J.D., Ph.D., Jerry Avorn, M.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

In March 2015, the Food and Drug Administration (FDA) approved filgrastim-sndz (Zarxio), Sandoz's version of the leukocyte growth factor Neupogen, an Amgen drug indicated for conditions including neutropenia in patients with nonmyeloid cancers and for stem-cell harvesting. Filgrastim-sndz is a follow-on biologic, a version of a protein-based drug made by a different manufacturer but approved for the same clinical indications; it was the first product in the United States authorized through the new regulatory pathway for follow-on biologics.

Biologics have provided major advances in the treatment of cancer, rheumatologic disease, and other conditions. Though they account for less than 1% of all prescriptions dispensed in the United States, expenditures on them amount to 28% of prescription-drug spending, and both their use and their cost are forecast to grow sharply. Payers have responded by imposing greater patient cost-sharing obligations and increased preauthorization requirements or have refused to cover certain biologics — moves that can result in substantial burdens for patients with chronic diseases.[1] Yet some of these drugs, such as filgrastim, have been on the market for decades and have no active-ingredient patents remaining to block competition from other manufacturers.

When market-exclusivity protections end for small-molecule drugs, interchangeable generics are approved through an abbreviated FDA pathway created by the 1984 Hatch–Waxman Act, which leads to major price reductions. A similar regulatory pathway for follow-on biologics did not exist until Congress passed the Biologics Price Competition and Innovation Act (BPCIA) as part of the Affordable Care Act in 2010. This pathway permits approval of follow-on biologics based on solid evidence of structural similarity, with only small confirmatory clinical trials — much smaller than the trials traditionally required for approving new drugs.

Two types of follow-on biologics can emerge from this pathway: biosimilars, products with no clinically meaningful structural differences from a brand-name biologic; and interchangeables, biosimilars that can be safely substituted for the original — a higher regulatory standard. Because the FDA has not yet clarified the level of evidence required for the interchangeable designation, most products initially approved under the BPCIA will be biosimilars, as filgrastim-sndz is. Other follow-on biologics being considered by the FDA include versions of infliximab (Remicade, first approved in 1998), pegfilgrastim (Neulasta, 2002), and epoetin alfa (Epogen, 1989). By contrast, follow-on biologic alternatives to several brand-name large-molecule drugs have been in use in Europe for years, although they are not automatically considered interchangeable.

The introduction of generic versions of small-molecule drugs can reduce prices by 90% from the brand-name version, which has saved U.S. consumers more

than $1.5 trillion over the past decade. Cost savings for biologic drugs, however, are inherently limited because they are more complex and therefore harder to produce than small-molecule drugs. This complexity raises the cost of development and reduces the number of potential market entrants. An FDA report showed that among generic small-molecule drugs, prices reach the maximum savings level only when 10 or more competitors are on the market[2] — an unlikely occurrence for many biologics. In the European Union, where 22 follow-on biologics are available, the median price savings for biosimilar epoetin alfa is just 35%.[3]

The evidence required for regulatory approval of follow-on biologics is also greater than that for generic small-molecule drugs — another market-entry hurdle. Small variations in biologic products may reduce efficacy or induce immunogenic responses. Such problems can even arise when the original manufacturer makes slight known changes (evolution) or unknown changes (drift) to its own production process,[4] which can then yield a product that diverges from its predecessor. The potential for divergence may be compounded among multiple manufacturers that lack access to each other's production processes. As a result, vigorous postapproval surveillance of biologics will be a major scientific and policy challenge in the coming years.

Savings from follow-on biologics may also be less than expected in the United States owing to hurdles such as the patent-dispute resolution process under the BPCIA. The BPCIA grants nearly all "innovator" biologics manufacturers a 12-year marketing exclusivity period, ensuring monopoly-like pricing during that time. This will apply to biosimilars and interchangeable biologics alike. By contrast, the Hatch–Waxman Act provides guaranteed exclusivity for only 5 years for brand-name small-molecule manufacturers, which must also provide the FDA with a list of the key patents protecting their products. Then, before obtaining marketing approval, generics manufacturers must certify to the FDA that they will not infringe these patents or show that the patents are invalid, which frequently leads to litigation between the brand-name and generics companies. The BPCIA's ambiguous patent-resolution process could be even more lengthy, costly, and convoluted. For example, some lawyers argue that the law mandates that follow-on biologics producers share their biosimilar applications with the original manufacturers to determine whether patents may be infringed. Because such disclosures could include trade secrets — nonpatented, company-specific information related to product development — the appeal of this approval pathway could be greatly diminished. Indeed, Sandoz refused to share its biosimilar application for filgrastim-sndz with Amgen, prompting a lawsuit. Although a federal district court recently ruled against compulsory biosimilar application sharing in that case, the decision is on appeal, and another challenge involving the same issue is pending for Celltrion's follow-on biologic infliximab.[5]

Meanwhile, U.S. postapproval factors may also hinder uptake of follow-on biologics. Whereas the European Medicines Agency permits biosimilars to use the same active-ingredient name as their brand-name counterparts, U.S. naming practices for these products are not set. In the interim, the FDA has required that Sandoz use the suffix "-sndz" for its version of filgrastim. This measure may help physicians and patients distinguish biosimilars, but it may also induce confusion among those expecting versions of the same product to share the same active-ingredient name, and it is not necessary for effective postapproval pharmacovigilance. For reimbursement of provider-administered biologics, payers customarily require a Healthcare Common Procedure Coding System "J code." The Centers for Medicare and Medicaid Services is currently considering requiring unique J codes for follow-on biologics under Medicare Part B. It should be strongly encouraged to do so; private payers would follow suit, and the requirement would facilitate rigorous, product-specific surveillance of biologics through the FDA's Sentinel system.

In addition, some manufacturers have been aggressively lobbying state legislatures to craft so-called carve-outs to drug-product-selection laws, which normally authorize or require pharmacists to substitute a lower-cost, interchangeable product when they receive a prescription for a brand-name drug. Such carve-out laws subject follow-on biologics to substitution policies that are less favorable than those for generic small-molecule drugs and have been enacted by eight states — Colorado, Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, and Utah. Such heightened barriers to substitu-

tion are likely to reduce the market penetration of interchangeable biologics.

The challenges to achieving savings from follow-on biologics are large but not insurmountable. First, market-entry hurdles should be low enough to ensure that enough companies compete to affect prices. Public investment in technological advances that can support biosimilar development, such as advancing knowledge about glycosylating human proteins in yeast, can aid all manufacturers. The FDA can help by promulgating product-specific guidance on how companies can demonstrate biosimilarity or interchangeability, to reduce the disadvantages for the first companies to try. Legislators may also need to reexamine the process for exchanging information about potentially infringing patents, to ensure that innovator manufacturers cannot unreasonably delay the process in order to extend their market exclusivity, and to prevent biosimilar manufacturers from entering into anticompetitive settlements. Such settlements have bedeviled the generic small-molecule drug industry but, since 2003, have had to be reported to the Federal Trade Commission for evaluation of their anticompetitive effects. This requirement may have to be extended to biologic drugs.

An audio interview with Dr. Kesselheim is available at NEJM.org

Innovative approaches will be required to ensure mandatory, rigorous postapproval research on the safety and effectiveness of biosimilars compared with their innovator predecessors in order to promote confidence in these new products. Over the long term, attention to both these areas will help ensure that U.S. patients benefit from appropriate price reductions for older biologic drugs that are essential for their clinical care. At the same time, fair but appropriately limited periods of exclusivity will reward the innovators of the original products while also spurring them to create new products rather than prolong exclusivity rights over older ones long after such monopolies should have come to a natural end.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.

This article was published on May 6, 2015, at NEJM.org.

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DOI: 10.1056/NEJMp1504672

No Place to Call Home — Policies to Reduce ED Use in Medicaid

Ari B. Friedman, M.S., Brendan Saloner, Ph.D., and Renee Y. Hsia, M.D.

One goal of Medicaid expansion under the Affordable Care Act (ACA) is to provide low-income, medically vulnerable adults with a source of care outside the emergency department (ED) and the means to pay for that care. Yet Medicaid expansion alone may not reduce ED use among new enrollees. Although some research suggests that Medicaid coverage is associated with reduced ED use, a lottery-based, controlled study from Oregon found that newly enrolled beneficiaries actually increased their ED use, at least temporarily.[1] This finding is not surprising, since health insurance reduces financial barriers to being seen promptly, and the