



## Balancing Innovation, Access, and Profits — Market Exclusivity for Biologics

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Twenty-five years ago, Congress enacted the Waxman–Hatch Act to facilitate the approval by the Food and Drug Administration (FDA) of low-cost generic drugs that are bioequivalent to

approved brand-name drugs. This law has been largely successful, in that generic drugs now account for more than 70% of prescriptions dispensed in the United States (and for 20% of dollars spent on medications). In most cases, a generic version becomes available immediately after the patent protection for a brand-name drug ends. This year, Congress is considering legislation to translate this approach to biologic drug products — larger, more complex molecules that are often produced from living cells. These agents, few of which existed in 1984, include many important new therapies and constitute the fastest-growing segment of the pharmaceutical market.

The Waxman–Hatch Act suc-

cessfully balanced the public interest in providing adequate incentives for investment in innovation with the public interest in providing affordable medications. It did so through three key provisions: the extension of pharmaceutical patent terms for up to 5 years to make up for time lost to regulatory review; a guarantee of 5 years of market exclusivity independent of any patent considerations; and the creation of a simple, inexpensive pathway for FDA approval of bioequivalent generic drugs. With these provisions in place, the research-based pharmaceutical industry has remained a leader in earnings growth and return on equity for its shareholders despite the dramatic increase in the use of generic drugs.

Biologics represent one of the most promising frontiers in pharmacotherapy, but their costs can be substantial, reaching \$200,000 or more annually for treatments such as imiglucerase (Cerezyme, Genzyme) for Gaucher’s disease (see table).<sup>1</sup> This past summer, committees in both the Senate and the House approved bills that would authorize the FDA to create an approval pathway for follow-on biologic, or “biosimilar,” products that would guarantee manufacturers 12 years of market exclusivity for a new biologic agent before any biosimilar product could be approved, even in the absence of a valid patent. Manufacturers could also obtain an additional 12-year exclusivity period by making minor changes to the structure of an approved product, such as those that could lead to changes in administration schedules (e.g., from weekly to monthly). Supporters argue that these much longer periods of

Cost to U.S. Consumers of Some Commonly Used Biologic Drugs.*		
Drug Name	Indication	Annual Cost \$
Etanercept (Enbrel, Amgen and Wyeth)	Rheumatoid arthritis	26,247
Trastuzumab (Herceptin, Genentech)	Breast cancer	37,180
Interferon beta-1a (Rebif, EMD Serono and Pfizer)	Multiple sclerosis	39,505
Adalimumab (Humira, Abbott)	Rheumatoid arthritis and Crohn's disease	50,933†
Imatinib (Gleevec, Novartis)	Leukemia and gastrointestinal stromal tumor	56,424†
Epoetin alfa (Eprex, Amgen)	Anemia of chronic renal disease	84,467
Imiglucerase (Cerezyme, Genzyme)	Gaucher's disease	200,000

\* Full cost estimates were annualized on the basis of a reasonable course of therapy for the given indication.

† Costs are for the treatment of Crohn's disease and gastrointestinal stromal tumors.

protection from competition are fair because the development costs for biologic products are higher than they are for other medications. However, the bills fail to recognize the unique characteristics of biologic drugs and upsets the delicate balance between the interests of consumers and those of innovators.

In many cases, we do not yet have the analytical tools to determine whether two biologic drugs are chemically or therapeutically identical. The FDA has made it clear that even an abbreviated approval pathway would require a great deal of independent data proving the safety and efficacy of a biosimilar product, including expensive immunogenicity studies and clinical trials.<sup>2</sup> In fact, there is no assurance that the proposed pathway to approval of a biosimilar product would be shorter or less expensive than a full Biologics Licensing Application (BLA) for a new product.

The proposed legislation would also impose additional hurdles before therapeutically similar follow-on biologics could be declared interchangeable. Currently, when a physician writes a prescrip-

tion for a brand-name small-molecule drug, state laws permit (or even require) pharmacists to automatically substitute bioequivalent generic drugs in nearly all cases. If biosimilar products are not similarly interchangeable with the original biologic product, they could not be substituted for the original and would have to be marketed to physicians as therapeutic alternatives. The cost of deploying a promotional program and sales force for this purpose would inevitably limit the number of potential market entrants and increase drug costs. In Europe, where mechanisms for introducing biosimilar products are already in place, approved products have won a relatively small initial market share and only modest price reductions, in the range of 25 to 30% as compared with up to 80% for other generic drugs.

Thus, even after all patent and exclusivity rights have expired and a biosimilar product is eventually approved, innovator companies would maintain a substantial revenue stream in the new system. The market for biosimilar products is likely to resemble that for new members of a chem-

ical class that already has established therapeutic value. Such markets differ from that for small-molecule generics, in which interchangeability creates intense price competition that swiftly reduces the market share of the expensive branded product.

One consequence is that there would be a positive premium for marketing the first or second biosimilar product. Even if the new legislation is adopted, manufacturers of potential follow-on products would probably prefer to ignore the new pathway and opt to file a standard BLA, which would not be subject to the 12-year delay. Any higher cost would be offset by the greater profit opportunity available to early market entrants. Therefore, as currently fashioned, the biosimilar legislation would have no value, because it would create a pathway that would scarcely be used. Innovators would not get the benefit of the exclusivity provision, and the public would not get the benefit of the enhanced price competition that would result from increasing the number of competitors.

In proposing a 12-year market-exclusivity period not tied to any existing patent rights, Congress is also ignoring the recommendations made in June by the Federal Trade Commission (FTC). The FTC concluded that innovative products should not receive additional market exclusivity beyond the term of their patents, because such a boon would "direct scarce [research and development] dollars toward developing low-risk clinical and safety data for drug products with proven mechanisms of action rather than toward new inventions to address unmet medical needs."<sup>3</sup> Manufacturers have disagreed, arguing that 12 years

of exclusivity are essential because it is easier to design around patents for biologic drugs than around those for small-molecule drugs. However, there is no evidence from the FDA or the courts substantiating that claim. For example, Amgen, the manufacturer of Epogen (epoetin alfa), has successfully prevented competitors from importing biosimilar erythrocyte-stimulating agents approved by European authorities by invoking patents covering both the product and the process for making it (notably, some original patents protecting the active ingredient have already expired). A federal Circuit Court of Appeals recently found that Amgen's broad patents are being infringed by a competitor's similar — but not identical — products and processes.<sup>4</sup>

In reality, the pharmaceutical industry's demand for a 12-year exclusivity period builds on one of the glaring failures of the Waxman–Hatch Act.<sup>5</sup> The act allows innovator companies to delay competition from generics for 30

months merely by asserting that their patents were infringed, even if this claim is not borne out. Manufacturers of brand-name drugs have responded by seeking and obtaining many patents of questionable validity, engaging in frequent and costly patent litigation, and using litigated patents as vehicles for settlements in which they pay the manufacturers of potentially competitive generics to refrain from challenging their patents. Congress is now considering additional legislation to prevent these abuses, which allow questionable patents to extend exclusivity improperly. For biologic products, innovators seek — and Congress seems willing to grant — an iron-clad 12-year exclusivity period that would essentially eliminate the need to defend any patents.

The full Congress can still revisit this issue. President Barack Obama should encourage amendments that would give the FDA the mandate to evaluate and approve biosimilar drugs in a reasonable period, starting, as with

small-molecule products, 5 years after the approval of the original drug. Such a compromise would best balance the need for financial incentives with the need for competition, promoting access and motivating important subsequent innovation.

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## GLOBAL HEALTH

# Defeating Rotavirus? The Global Recommendation for Rotavirus Vaccination

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This past April, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization announced a global recommendation that rotavirus vaccines be included in national immunization programs. The basis for the decision is clear: more than 2 million children younger than 5 years of age are hospitalized each year because of rotavirus gastroenteritis, and more than half a million of them die. The introduction of rotavirus vac-

cines into national immunization programs in the United States, Europe, Latin America, and Australia has already caused a significant decline in hospitalizations and emergency department visits for rotavirus disease.<sup>1</sup> The onset and peak of the 2008 rotavirus season in the United States were delayed, and the number of positive rotavirus tests decreased by 67% as compared with the number in the prevaccine years of 1991 through 2006.<sup>2</sup> However, 86% of deaths due to rota-

virus occur in Africa and Asia (see map), where the potential benefits of rotavirus vaccines may be the greatest. But the paucity of data on efficacy in regions with high mortality among children younger than 5 years of age, the cost of vaccination programs, and other implementation challenges have hindered the broadening of immunization efforts to countries in Africa and Southeast Asia.

So how effective will rotavirus vaccines be in these countries? Ac-