

PERSPECTIVE

Encouraging The Development Of New Vaccines

R&D subsidies for new drugs to treat rare diseases are much larger than those for new vaccines to prevent more common diseases.

by Henry Grabowski

ABSTRACT: Investment in the development of new vaccines is suboptimal. Changing this situation requires a creative blend of “push” and “pull” strategies. One successful policy model is the Orphan Drug Act, whose key features include large research and development (R&D) tax credits as well as Food and Drug Administration (FDA) counseling and priority review. Such supply-side R&D incentive provisions can be combined with demand-side mandates and vouchers to encourage development of new vaccines. Guaranteed-purchase funds and other pull mechanisms are useful supplementary incentives in the cases of vaccines for bioterrorism and neglected diseases of poverty.

MARK PAULY does a good job of analyzing the tensions and conflicting incentives across various constituent groups in the supply and development of vaccines.¹ I focus my comments here on issues and policies relating to the development of new vaccines. In an earlier analysis, John Vernon and I found that vaccines were characterized by rich scientific opportunities at the discovery level and important efforts in the early clinical phases.² However, vaccine innovation has been hampered by the need for large up-front spending on clinical trials and plant facilities combined with uncertain prospects for economic returns. Vaccine revenues and prices are increasingly driven by government purchasing programs designed to minimize public spending. This has amplified these economic uncertainties.³

IOM Proposal: A ‘Pull’ Strategy

Given vaccines’ favorable public health properties, there is reason to believe that there is underinvestment in new vaccine develop-

ment under U.S. institutional and policy regimes. The Institute of Medicine (IOM) proposal for a publicly funded mandate and a precommitment to price new vaccines in proportion to their social benefits addresses this underinvestment.⁴ From an economic incentive perspective, the proposal contains many laudable features. If implemented, it would lead to larger markets, higher margins, and an increase in private research and development (R&D) investments.

■ **Time problem.** One potentially serious flaw in the IOM proposal is the time inconsistency problem. The R&D process for new vaccines and drugs generally takes more than ten years, requires high up-front spending, and is subject to high rates of project attrition.⁵ The proposal therefore raises the problem of how to precommit future government bodies to a pricing process that is creditable to current R&D investors. In a different context, Michael Kremer and colleagues have suggested approaches to solving this problem for a malaria vaccine that involve escrow accounts or other

Henry Grabowski (grabow@econ.duke.edu) is a professor of economics at Duke University in Durham, North Carolina.

contractual arrangements.⁶ Whether this would work in the current context, given the scale and scope of the IOM proposal, remains debatable.

■ **Potential impact on prices.** Given the current public climate regarding drug prices and profits, it is easy to see how, if the IOM proposal were enacted, high vaccine prices for socially beneficial vaccines could become a focus of future federal policy deliberations.⁷ One could envision government budgetary pressures combined with the appearance of windfall profits on vaccines leading to a downward spiral in prices. This would lead to a lower percentage of the social benefits being covered than initially projected to developers of new vaccines. This possibility could then undercut the credibility of the program to prospective innovators. The likely focus on budgeted distributional consequences is consistent with the different perceptions and objectives of the various stakeholder groups discussed in Pauly's paper.

Orphan Drug Act: 'Push' And 'Pull' Strategies

Other alternatives to increase R&D investment in vaccines could involve push strategies that subsidize research inputs or lower R&D costs. One successful policy measure involving both push and pull mechanisms is the Orphan Drug Act (ODA) of 1983. It was designed to increase R&D investment incentives for rare diseases and illnesses—those with a prevalence of fewer than 200,000 U.S. patients.⁸

The ODA contains three provisions to lower R&D costs. First, it establishes a 50 percent tax credit on clinical trials for orphan drug indications. Second, it includes a modest clinical research grant program targeted to the earlier stages of development. Third, it requires FDA advice and counseling to sponsors on acceptable research protocols for orphan drug development. These R&D push provisions are combined with one pull incentive: a guaranteed seven-year market exclusivity that runs concurrently with any patent-exclusivity terms applicable to particular drugs.

■ **Potential principal-agency problems.**

While pull strategies have time inconsistency issues, push strategies are subject to potential principal-agency problems. In particular, push mechanisms that subsidize research inputs are subject to problems of asymmetric information and moral hazard incentive. This is particularly true if government officials determine what projects should be funded through a centralized decision-making process.⁹ However, the ODA's primary incentive of a 50 percent tax credit is designed to moderate these problems. In particular, the developers of designated orphan drugs still have to put up 50 percent of the funds for the clinical trials. Furthermore, the program operates in a decentralized market fashion rather than relying on a centralized funding approach in which government officials pick the winners and losers.

■ **Impact on new drug approvals.** The FDA states that "more than 200 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to market."¹⁰ As of December 2004, the FDA had granted 1,432 orphan drug designations to pharmaceutical compounds, making the clinical trials for these orphan indications eligible for tax credits and other benefits. In addition, there have been 265 orphan drug approvals.¹¹ Almost half of these approvals have been for new molecular entities (NMEs) or new biopharmaceuticals.¹²

These data suggest a similar probability of success for orphan drug approvals as that for nonorphan indications. In particular, FDA data indicate that 18.5 percent of total orphan drug designations are approved. This compares with a 21.5 percent probability of success observed by Joseph DiMasi and colleagues for drugs entering clinical trials in the 1980s and early 1990s.¹³

■ **Smaller trial sample.** An analysis of data from several orphan drug approvals also indicates that fewer subjects are typically needed for FDA approval than is the case for nonorphan drugs.¹⁴ It is probably infeasible to approve vaccines on the basis of smaller clinical trial populations, given their administration to large populations after approval. How-

ever, push strategies such as substantial R&D tax credits, FDA counseling on acceptable protocols, rolling submissions of applications for marketing approval, and priority review of the clinical trial data seem appropriate for vaccines with high expected benefit costs and cost-effectiveness properties.

■ **Revenues.** An analysis of the revenues of orphan drugs introduced in the early 1990s indicates that sales after ten years on the market for new orphan drugs are only about one-fifth of those for nonorphan indications. The majority of orphan drug introductions had peak-year sales well below \$100 million in value.¹⁵ Clearly, the application of the R&D tax credit and special FDA approval provisions have been instrumental in lowering R&D costs and encouraging increased investment in drugs for orphan indications with limited market sales.

One area where the ODA has not provided very strong incentives is new drugs and vaccines for the neglected diseases such as malaria and tuberculosis that affect poor countries. Given their low prevalence in the United States, diseases that predominantly affect poor countries are technically eligible for all of the incentive provisions of the ODA. However, developing countries lack the resources to afford these medicines, with many devoting as little as \$2 per capita per year to health care.¹⁶ Hence, some form of pull mechanism becomes a necessary complement to the ODA to increase R&D incentives.

The Pull Mechanisms Working Group has proposed a guaranteed purchase fund for a new malaria vaccine.¹⁷ Using funds from philanthropic sources, the purchase fund is designed to provide a competitive market return to the innovator. However, the vaccine would be distributed for a modest copayment in eligible developing countries. Another pull mechanism that has been analyzed in this context involves a voucher for priority review of a new drug application of a company's choice in exchange for developing a drug for a neglected disease that is made freely available to all producers.¹⁸

Project Bioshield: 'Push' And 'Pull' Incentives

Vaccines and drugs to address bioterrorism threats is another case in which existing markets are unable to sustain long-term R&D efforts. The U.S. Congress recently approved the Project Bioshield Act of 2004. It contains both push and pull incentives to deal with bioterrorism threats such as anthrax, ebola, and smallpox. The legislation authorizes a \$5.6 billion government fund over a ten-year period to purchase vaccines and drugs that will be stored in a strategic national stockpile.

A key pull mechanism in Project Bioshield is that the government can enter into contracts up to eight years before expected FDA licensing.¹⁹ At this point, however, there are several concerns that affect its long-term credibility to innovators: how prices will be determined, how the specifications of the final product will be defined to earn Bioshield's contractual payments, and concerns about liability, patents, and opportunity-cost issues.²⁰

AS PAULY'S PAPER EMPHASIZES, any proposal designed to improve R&D incentives for new vaccines must receive support from important shareholder groups. This will likely require a creative blend of push and pull strategies. It is ironic that R&D incentives for rare diseases receive large subsidies and priority treatment in the United States, whereas those for vaccines with broad-based social benefits are suboptimal.

The Orphan Drug Act could be a useful model for vaccines, particularly from the perspective of political and economic feasibility. R&D tax credits as well as FDA counseling and priority treatment have been its key components. They could also be key elements of a new public program to stimulate R&D investment in vaccines. This could be combined with federal mandates and vouchers on the demand side to insure higher utilization levels. Under this approach, the government would continue to be a major purchaser of vaccines alongside the private sector. Negotiated prices for new vaccines would presumably reflect

both R&D subsidies and expected social benefits. Guaranteed purchase funds and other pull mechanisms could be available as supplementary measures for special circumstances such as diseases of poverty and for bioterrorism threats where markets are limited or non-existent.

.....
The author is indebted to Bob Cook-Deegan, Jeff Moe, and Kevin Schulman for many insightful discussions and references on public health questions and issues.

NOTES

1. M.V. Pauly, "Improving Vaccine Supply and Development: Who Needs What?" *Health Affairs* 24, no. 3 (2005): 680-689.
2. H. Grabowski and J. Vernon, *The Search for New Vaccines: The Effects of the Vaccines for Children Program* (Washington: AEI Press, 1997).
3. Institute of Medicine, *Financing Vaccines in the Twenty-first Century: Assuring Access and Availability* (Washington: National Academies Press, 2004).
4. *Ibid.*
5. Joseph DiMasi and colleagues have estimated that the average capitalized R&D cost to develop a new drug is \$802 million. Given the large number of subjects required for vaccine trials and the high plant investment costs, the total cost of developing a new vaccine is presumably at least as great as that for a new drug. J. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151-185.
6. M. Kremer, "Pharmaceuticals and the Developing World," *Journal of Economic Perspectives* 16, no. 4 (2002): 67-90; and M. Kremer, "Creating Markets for New Vaccines, Part II: Design Issues in Innovation Policy and the Economy," in *Innovation Policy and the Economy*, ed. A.B. Jaffe et al. (Cambridge, Mass.: MIT Press, 2001), 73-118.
7. See, for example, U.S. Department of Health and Human Services, Office of Inspector General, "Review of Epogen Reimbursement," Pub. no. A-01-92-00506 (Washington: U.S. Government Printing Office, January 1993). In 1993 the inspector general's staff recommended a lower reimbursement rate for Epogen that focused in part on Amgen's apparent high profits.
8. S.R. Shulman et al., "Implementation of the Orphan Drug Act: 1983-1991," *Food and Drug Law Journal* 47, no. 4 (1992): 363-403.
9. See, for example, Kremer, "Pharmaceuticals and the Developing World," 82-86.
10. U.S. Food and Drug Administration, Office of Orphan Products Development, "Brief History of the Office," June 2000, www.fda.gov/orphan/history.htm (4 March 2005).
11. FDA, "Cumulative List of Orphan Products Designated and Approved," www.fda.gov/orphan/designat/allap.rtf (4 March 2005).
12. H. Grabowski, "Increasing R&D Incentives for Neglected Disease: Lessons from the Orphan Drug Act," in *International Public Goods and Transfer of Technology under a Globalized Intellectual Property Regime*, ed. K.E. Maskus and J.H. Reichman (Cambridge: Cambridge University Press, 2005).
13. DiMasi et al., "The Price of Innovation."
14. Grabowski, "Increasing R&D Incentives."
15. *Ibid.* The sales distribution of orphan drugs is highly skewed. Although most of them have very modest sales, a few very expensive biopharmaceutical orphan drugs have more than \$1 billion in annual sales. This is comparable to top-selling pharmaceutical products.
16. Grabowski, "Increasing R&D Incentives."
17. R. Levine et al., *Making Markets for Vaccines* (Washington: Center for Global Development, 2005).
18. D. Ridley, H. Grabowski, and J. Moe, "Developing Drugs for Developing Countries" (Unpublished manuscript, Duke University, January 2005).
19. F. Gotttron, "Project Bioshield," CRS Report for Congress, 27 December 2004, www.usembassy.it/pdf/other/RS21507.pdf (28 March 2005).
20. See, for example, A. Towse and H. Kettler, "Advance Price or Purchase Commitments to Create Markets for Diseases of Poverty: Lessons from Three Policies," *Bulletin of the World Health Organization* (forthcoming); and Chemical and Biological Arms Control Institute, *Meeting the Biodefense Challenge: A "Roadmap" for a National Vaccine Strategy*, Report of the CBACI National Vaccine Strategy Working Group, September 2004, www.cbaci.org/pubs/reports/vaccineroadmap.pdf (28 March 2005). An oft-cited example, where long-term credibility issues were created by a government action, is the threat against Bayer in fall 2001 to negate its ciprofloxacin patent unless it reduced the price.

Copyright of Health Affairs is the property of Project HOPE/HEALTH AFFAIRS and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.