

The Merck Company
Foundation
Program on
Pharmaceutical
Policy Issues

Incentives for Innovation: New Perspectives

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The Merck Company Foundation

Program on Pharmaceutical Policy Issues

Merck's mission is to improve the health and well-being of people worldwide through the discovery, development, and manufacturing of innovative medicines and vaccines that enhance global health and overall quality of life. We have vigorously pursued this mission for more than a century and remain committed to turning breakthrough science into novel medicines that represent real advances in patient care.

To help achieve this overall mission, Merck fosters the advancement of health policy research and scholarship in health economics and related disciplines to create a strong foundation for informed public policy making and global dialogue regarding health systems. Merck believes that academe plays a critical role — through research, education and public outreach — in shaping healthcare systems.

Merck's Program on Pharmaceutical Policy Issues (PPPI)

Launched in 1999, The Merck Company Foundation's Program on Pharmaceutical Policy Issues provides an opportunity for academic institutions worldwide to develop centers of excellence in pharmaceutical and health policy. It enables institutions to enhance their capacity in research, teaching and dissemination through three-year renewable grant programs.

Merck's PPPI seeks to encourage research in the following areas:

- Access to medicines and biomedical innovations in the developing world
- Economics of the pharmaceutical industry, including incentives and disincentives for innovation
- Evaluation of new therapies, health care technology and biomedical innovation

- Evolving market characteristics and changing market dynamics for pharmaceuticals, including competition and pricing
- Global issues affecting healthcare quality and patient access
- Analyses of factors that contribute to sustained innovation in the pharmaceutical industry
- Effect of healthcare financing strategies and reimbursement policies on pharmaceuticals and patient access
- Regulatory and industrial policy issues, including intellectual property and global trade issues
- Consumer health promotion strategies

Selection of PPPI centers of excellence is based upon a competitive application and review process. This process is informed by the recommendations of an independent Academic Advisory Board, which includes international experts in public health, economics, public policy and health services research. To date, Merck's PPPI has provided more than \$7 million in grant support toward programs at the Columbia University and Stanford University Consortium, Cornell University, Fu Dan University, Institute for Health Economics, London School of Economics, Massachusetts Institute of Technology, University of Arizona—School of Pharmacy, University of Costa Rica, University Carlos III de Madrid / University Pompeu Fabra de Barcelona Consortium, University of Siena, Victoria University, and the Wharton School at the University of Pennsylvania.



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Executive Summary

This is the second PPPI policy conference since the inception of the program. The theme, *Incentives for Innovation*, provided a unique opportunity to learn more about the work at each PPPI center. It also offered researchers a forum to share ideas on emerging policy issues and identify potential areas of new research.

One key issue facing society and industry is achieving the appropriate balance between innovation (which provides global benefits) and the need for cost containment within each country. During these discussions, the group identified differences in what people meant by **access** to new medicines. Some thought access meant that the medicine existed and was available at the pharmacy. Others thought access meant that people (or governments) could get medicines at “affordable” prices. Clearly, these viewpoints represent differences in fundamental values across countries and cultures. But must there be a trade-off between price and innovation, or is it possible to have new innovative medicines at affordable prices?

Regulation and Innovation

The first set of papers addressed the topics of regulating innovation and innovating regulations, with papers from the PPPI programs at the Columbia/Stanford Consortium, University of Siena, the Institute for Health Economics, Fu Dan University, and the Wharton School. A critical issue is achieving a balance between the incentives for firms in the pharmaceutical and biotechnology industry to invest in research and development (R&D) projects and the need for society to manage and control the expenditures on healthcare in the aggregate, and on pharmaceuticals in particular. Joshua Graff-Zivin and colleagues (Columbia) are looking at the question of how various nations use different mechanisms to manage these competing objectives. Fabio Pammolli (Siena) provides a theoretical model to examine the question of how regulations affecting the returns on the most successful products might affect the size and growth of the industry over the long run.

On a more concrete level, Devidas Menon, at the Institute for Health Economics, is looking at how regulatory reforms in Canada are streamlining the process and decreasing the burden placed on firms registering a new drug. On the other side of the world, Shanlian Hu (Fu Dan) is looking at the ways China is trying to move towards a market

based healthcare system, and towards the establishment of private health insurance as a mechanism to increase access to newer medicines and other healthcare services.

Back in the United States, Alan Mathios (Cornell) and his research team are looking at the role that direct-to-consumer advertising can have on increasing the incentives for firms to innovate. His team is examining the role advertising plays in the smoking cessation market. Specifically, they look at how Food and Drug Administration (FDA) regulation has affected the number of smoking cessation advertisements consumers are exposed to. They find that regulations have an important impact and that advertising increased when these products moved to over-the-counter status. Their goal is to determine whether advertising leads to a decrease in the rate of smokers. And Mark Pauly (Wharton) is focusing his efforts on the question of how work-loss is factored into the cost-benefit and cost-effectiveness analysis used in some countries as the basis for establishing a product's price.

Innovation and Industry

For the pharmaceutical industry, the decade of the 1990s was characterized by two dominant features. First is an apparent decline in R&D productivity. During the decade, private spending on R&D more than doubled from \$20 billion to \$46 billion; while the number of new chemical entities filed with the U. S. Food and Drug Administration fell from 40 to 26 per year¹. This downward spiral continues into the current decade. Second, the industry went through a series of mergers among the larger pharmaceutical firms (in an effort to achieve economies of scale and scope), while at the same time there was the emergence of a larger number of highly specialized, small, start-up biotechnology firms.

Understanding the interplay between technology, innovation, and industry structure was the topic of the second group of papers, which featured studies by the programs at the Massachusetts Institute of Technology and Victoria University. Stan Finkelstein, at MIT, is working on the productivity question by examining the development of oncology drugs over the decade of the 1990s. He is finding evidence that

¹ Bolten, B., DeGregorio, T. “Trends in Development Cycles” *Nature Reviews*, 1 (May 2002): 335-336.

coincident with the penetration of some of the newer technologies, the safety profiles of the newer drugs under investigation have improved significantly compared to the older ones. However, he has not observed the same trend for efficacy. Peter Sheehan (Victoria) is looking at the evolving structure of the pharmaceutical industry, in particular the technology transfers across firms around the world. He is finding significant increases in the use of alliances as a mechanism by which larger pharmaceutical companies are gaining access to the newer technologies created by smaller biotechnology firms.

Competition and Market Dynamics

Competition in the pharmaceutical industry takes place at many levels. It takes place in the race to develop and introduce new classes of products, it takes place in the sales and promotional efforts of firms competing with different branded products in the same class, and it takes place between branded and generic products after patent expiration.

The final set of the prepared papers focused on the topic of Competition and Market Dynamics, with contributions from the PPPI programs at University Pompeu Fabra de Barcelona, Victoria University, University Carlos III de Madrid, London School of Economics, and the University of Costa Rica. These papers focused on specific aspects of the way firms compete in this industry.

Pedro Marin (Carlos III) presented a paper looking at the way branded firms compete and the impact that competing in multi-markets might have on the firm's incentives for more or less aggressive behaviors. Peter Sheehan looked at the pricing of branded products over time, and the impact of generic entry into the Australian market. He found significant price erosion during the early patent period and that generics had relatively little impact when they entered the market. Antonio Cabrales (Pompeu Fabra) presented a product differentiation model of brand-generic competition that helps to explain the apparent anomalies observed by comparing across countries with greater and lesser regulation. Panos Kanavos (London School of Economics) presented empirical work looking at the brand-brand and brand-generic competition in the UK, France, Germany and the Netherlands. He found significant price effects in the brand-brand competition, and showed that generic entry had a large impact on the branded market shares, but the impact on branded prices varied across countries. Juan Rafael Vargas (Costa Rica) and colleagues are examining price variation introduced by

wholesalers across Costa Rica, El Salvador, Guatemala and Nicaragua, and across retail outlets within Costa Rica. He presented data showing that even without manufacturers introducing price differences, local market conditions resulted in significant price differences both across and within countries.

Open Discussion

Throughout the meeting there were numerous opportunities to discuss issues that went beyond the scope of the current research reports. These included a discussion about the sustainability of the current structure of international prices, and whether US citizens are paying too much for their medicines or other countries are paying too little. Others focused on questions of international trade, the protection of intellectual property rights, and the importance of studying the impact of the pharmaceutical industry on economic growth.

Regulation and Innovation

Innovation is at the core of the pharmaceutical industry. Companies discover and patent compounds in hope that they will be useful medicines. If clinical trials successfully demonstrate safety and efficacy to the national regulatory agencies, pharmaceutical companies launch these products into a complex and highly competitive international market with overlapping rules and regulations. After several years, their patents expire and generic competitors can introduce copies and capture a significant share of the market with lower prices. Thus, pharmaceutical companies operate in the dynamic environment Schumpeter envisioned when he wrote of “creative destruction.”² Pharmaceutical firms must reinvent themselves every few years as the products in their portfolios turn over. This cycle is fueled by the billions of dollars spent annually on research and development. The existing standards of intellectual property protection and market segmentation allow the industry to earn sufficient returns on its most successful products to afford the risky and uncertain investments in the future generations of new products^{3,4}.

Changing regulations can affect future returns and potentially alter these incentives. The issues of how society values these new products, and what impact regulations have on their adoption and diffusion into the market are central to the policy debate. This session focused on how regulations are evolving and the potential implications for the pharmaceutical industry. In general, governments are moving beyond safety and efficacy issues and are now focusing on broader economic concerns, such as cost-effectiveness. In some cases, these changes are leading to fundamental reforms in the way healthcare is paid for and delivered.

Regulating Innovation

Joshua Graff-Zivin presented *Management of Technological Change: A Cross National Perspective* from the Columbia/Stanford Consortium. Their paper reviews the mechanisms that governments and regulators use to manage innovation in healthcare. On the supply side, these include restrictions on the adoption of new technology, such as pre-marketing controls, planning tools, and hospital and manpower planning programs. On the demand side, budget and reimbursement tools are used to control how much is spent on healthcare, and clinical guidelines are used to manage what services are provided. Of special interest is how governments

use cost effectiveness as a basis for decision making. Graff-Zivin and his colleagues assert that, “quantitative data can never be the sole source of social judgments: culture, ethics, psychology and politics complicate the equation with their own irreducible claims” They believe that by understanding how countries vary in their use of quantitative information, they can better understand how both quantitative and qualitative data influence policy makers.

Fabio Pammolli and colleagues at the University of Siena presented a theoretical paper on *Innovation, Growth and Market Regulation*. Their analysis focuses on the distribution of firm size and growth rates, and their goal is to find a fundamental law of how things grow, be it a firm, country or population. They use a relatively simple statistical model, and found that with appropriate parameters they can generate distributions of size and growth rates similar to the pharmaceutical industry. They also experimented to see what would happen if regulations were introduced that limited the upside of the distribution of opportunities. Their results suggest that such regulations could have a dramatic effect on the rate of innovation and the resulting distribution of firm size⁵.

Innovating Regulation

Devidas Menon and colleagues at the Institute for Health Economics are closely monitoring changes in the Canadian regulatory environment. Their paper, *Health Technologies in Canada: Reimbursement Challenges*, examines how the Canadian Health System is eliminating duplicative provincial health technology assessments by providing one national assessment. However, provincial governments still make critical decisions on product approval and reimbursement, so it is not clear whether they will abide by the national assessment or require independent, redundant

² Schumpeter, J. *Capitalism, Socialism and Democracy*. New York: Harper 1975 [orig. pub. 1942], pp: 82-85.

³ Grabowski, H., Vernon, J. “Effective Patent Life in Pharmaceuticals”. *International Journal of Technology Management* 19 (2000): 98-120.

⁴ Cockburn, I., Chwelos P. “Intellectual Property Rights and the Transition to the Knowledge-based Economy.” *In Doing Business in the Knowledge-based Economy*, ed. L. Lefebvre (New York: JAI Press, 2001).

⁵ De Fabritiis, G., et al. “On Size and Growth of Business Firms”. *Physica A* 324 (2003): 38-44.

reviews. They are keeping a close eye on this issue and will report back on their findings.

Shanlian Hu, Fu Dan University, provided a stimulating glimpse at the changes China is making to modernize its healthcare system. In ***Promoting Sustainable Development of Health and Pharmaceutical Industry to Foster Economic Development: Tripartite Sector Reform in China***, Hu and colleagues describe the interrelations among the responsibilities involving the Ministries of Health, Ministry of Labor and Social Security, and the State Development and Reform Commission. The group is conducting a social experiment by offering alternative forms of supplemental health insurance as a means of understanding consumer preferences. Preliminary results suggest that many people in China are dissatisfied with their current health insurance and welcome the opportunity to purchase additional insurance. Given the wide range in health needs, family income levels and personal preferences, the authors suggest that several plans should be offered and encouraged by the use of "tax deductions, price subsidies or personal medical savings accounts."

Alan Mathios and the team at Cornell University are interested in the regulation of direct-to-consumer (DTC) advertising. Their paper, ***Regulating Advertisement: The Case for Smoking Cessation Products***, provides a background on the history of health claims advertising. They observe that advertising has led to a dramatic increase in the number of "healthy" brands available. They also point to the dramatically different standards applied by the Federal Trade Commission and the Food and Drug Administration as a potential barrier to DTC advertising for prescription drugs. Given the negative health effects of smoking, it is ironic that smoking cessation ads face greater scrutiny than tobacco ads! After constructing an extensive database of advertising for both cessation and tobacco products, Mathios' preliminary analysis suggests that the loosening FDA standards and the movement from prescription to over-the-counter status resulted in a significant increase in advertising. Whether this increase leads to more Americans successfully quitting is the subject of further research for this program.

Mark Pauly and colleagues at the Wharton School have been working on a paper titled, ***Estimating the Real Cost of Workdays***, which measures the impact of work loss. In traditional cost-effectiveness analyses, when work-loss and productivity effects

are considered, they are typically valued as the lost time at the prevailing wage rate. In Pauly's model, they consider situations in which the loss of a single employee might have a larger impact. They believe that when workers are part of a team and when substitute workers are not perfect replacements, or when the output is time sensitive, the value of the work loss might be significantly greater. To test this hypothesis, they surveyed managers from a range of industries. Their results confirmed their hypotheses and have enabled them to develop wage-multipliers to estimate the impact of work loss. These multipliers have face validity: e.g. mechanical and aerospace engineers had a very high multiplier (about 2.5), while fast food workers had a very low multiplier (1.05). Although additional research is needed, the authors believe that these measures help to establish a new paradigm for incorporating Productivity-Adjusted Work Loss (PAWLy) into standard cost-effectiveness analyses.

PPPI researchers are examining the way societies value and reward innovation, and how regulations affect the underlying incentives for product development. As governments grapple with rising healthcare costs, due in part to technological change, the question of how society should value these changes will continue to be at the forefront of the debate.

Innovation and Industry

The data on corporate research & development spending and new pharmaceutical product introductions suggest that the productivity of the pharmaceutical industry fell dramatically during the 1990's. From 1985 to 2002, industry spending on R&D increased nearly four-fold, to over \$50 billion, yet the number of new chemical entities fell from a high of 62 in 1986 to a low of 17 in 2002.⁶ Understanding whether these trends represent a temporary drought in the drug pipeline or a fundamental shift is the subject of much debate.

In addition to the technological shift from molecular chemistry to genomics and proteomics, there are other structural changes happening. Thirty years ago, the new product pipeline was driven primarily by internal company research. Now, some firms are specializing in areas of discovery and development, and companies are leveraging external research through licensing agreements, alliances, and mergers and acquisitions with companies around the globe^{7,8}. How these technological and structural changes affect the incentives and rate of innovation are among the issues being addressed by the PPPI programs at MIT and Victoria University.

Technology and Innovation

Stan Finkelstein at MIT presented *Toward an Understanding of the Drivers of Successful Drug Development*. He and his colleagues are interested in the question of why the pace of drug discovery and development has not changed despite new technologies. Currently there are four (not necessarily competing) hypotheses for why the newer technologies have not delivered the promised medical breakthroughs.

- The easy drugs have already been discovered.
- New drugs, particularly for “complex” diseases, require new approaches to measurement and new endpoints.
- There is a long lag between the initial, enabling scientific advances and the introduction of new products.
- A “convergence” between multiple scientific and technological advances is required before the full benefits of one technology can be fully realized.

Their current research seeks to evaluate these explanations by focusing on product innovation in the area of oncology. They are examining published clinical trials over the past 15 years to determine whether there are indications that drug development is getting “better.” As evidence of improvement, they are hoping to find that newer drugs are safer, more effective, take less time to develop, enroll fewer people in clinical trials and, if failing, are discontinued earlier in the development cycle.

Although the work is just beginning, Finkelstein and colleagues have reviewed over 2400 abstracts from clinical trials, and have noted a dramatic rise in the number of Phase I and II clinical trials since 1990. They have also found a rise in commercial sponsorship for these early trials and an increase in the number of trials conducted outside the US. Most importantly, they have found a dramatic increase in the proportion of studies involving oral compounds, which are generally easier for patients to take. Moreover, although they found seemingly contradictory evidence that the response rates in these trials were declining, they also found evidence that the death rate among participants was dramatically lower. They tentatively conclude that advancing science and technology are increasingly being used in cancer drug development, that the newer drug candidates appear to be safer and less toxic, but that the newer drugs appear to offer little or no incremental improvement in efficacy. Their efforts are moving to a quantitative phase and they expect to have more definitive conclusions soon.

Technology and Industry Structure

Peter Sheehan and his colleagues at Victoria University have been focusing on understanding the evolving structure of the pharmaceutical and

⁶ Sinskey, A. “Healthcare and the New Biology Challenges and Opportunities.” Deshpande Center Ideastream Symposium, Program on the Pharmaceutical Industry, Massachusetts Institute of Technology, http://web.mit.edu/deshpandecenter/downloads/presos/ideastream2003_sysbio3.pdf (accessed on 30 August 2004).

⁷ Cockburn, I., and Henderson, R. “Scale and Scope in Drug Development: Unpacking the Advantages of Size in Pharmaceutical Research.” *Journal of Health Economics* 20 (2001): 1033-1057.

⁸ Galambos, L., Sturchio, J. “Pharmaceutical Firms and the Transition to Biotechnology: A Study in Strategic Innovation.” *Business History Review* 72 (Summer 1998): 250-78.

biotechnology industries. Their paper, *Innovation and Industry: Implications for Structure Pricing and Industry*, investigates the complex web of relationships among firms. During the 1990s, biotechnology emerged as a source for innovation in medicines. These technologies have focused primarily on 1) expanding the range of drugs available to treat diseases and 2) improving the efficiency of drug discovery (so-called platform technologies). These technologies have been developed primarily by specialized start-up firms, and large pharmaceutical companies have sought access to them through alliances, service contracts, and acquisitions. Sheehan and his colleagues have been monitoring the regional patterns in these alliances, looking at the flow of funds and technologies among the US, Europe, the UK, Canada, Japan and Australia. As one might expect, the US dominates much of the activity, with over 50% of all transactions involving a US company as either a buyer or a seller of technology. However, they also find that Canada has been serving a strong role as a technology developer for the US, with 106 alliances between Canadian developers and US buyers in 2001-03. European and British companies, on the other hand, are much more likely to be buyers of technology developed in the US. Somewhat surprisingly, Japan has had a low level of alliances, representing only 0.1% of the developer funds received. In Australia, there is a relatively low level of alliances among firms within the country, and a relatively high level of activity with companies outside Australia, particularly with US companies.

They conclude that there has been a rapid increase in the number of alliances across firms, particularly among biotech companies. These alliances initially were focused on platform technologies, but more recently there has been an upsurge involving drug development technologies. There is an increasing emphasis on genomics and genome related technologies. Interestingly, the business models continue to evolve and no dominant form has emerged.

It is crucial for policy makers to understand how drug development technology is changing and the consequence this has on R&D productivity, the rate of innovation and the structure of the industry. The PPPI programs are advancing our understanding of these fundamental issues. Conventional wisdom suggests that these newer technologies are not delivering the anticipated leap forward in developing new medicines, and that the process of drug development has become more costly and

more risky. The preliminary data from MIT suggest that this might not be the case. By using the newer technologies, clinical trials are becoming safer and better, for oncology drugs under development. At the same time, these new technologies are transforming the structure of the industry. Starting in the late 1980s, there has been a boom in the number of small, start-up biotechnology firms. Some have managed to grow into the equivalent size and structure as the larger pharmaceutical companies. Others have pursued a different business model and have struck alliances with larger companies. How the industry will ultimately align itself remains an intriguing question, as the roles that existing companies play in the process of drug discovery, development, manufacturing, and sales and marketing continue to evolve.

Competition and Market Dynamics

Competition in the pharmaceutical industry occurs on many levels. Firms compete to be the first to introduce a product in a new therapeutic class. Initially sales and marketing efforts focus on building disease awareness and often enable the entrant to establish a dominant position that can be maintained for a long time. As more firms enter, competition from new products lead to increasing branded promotional activities and pressure to reduce prices and offer discounts or rebates. In the US and New Zealand, branded direct-to-consumer advertising is also permitted. These efforts often lead to an expansion in the use of new products as more patients and physicians become aware of the products and the advantages they bring. As patents expire, generic competitors enter the market, frequently at much lower prices, and rapidly capture a large share of the market.

Because of laws prohibiting non-manufacturers from importing or exporting pharmaceutical products, most of these competitive dynamics take place within national boundaries. The result is market segmentation along national lines and prices that vary across countries based on market and regulatory conditions in each country. However, in the European Union (EU) licensed wholesalers are permitted to ship pharmaceuticals to locations within the various member states. This has put pressure on price differences within the EU countries, creating market distortions due to the incompatibility of the free movement of goods and national pricing and reimbursement controls on prescription medicines. There is a growing movement in the United States to permit the legal importation of pharmaceutical products from Canada and other countries. PPPI program participants are studying many of these competitive issues and are in a position to help inform the debate.

Pedro Marin and colleagues at University Carlos III de Madrid are looking at the implications of **Multi-market Contact in Pharmaceutical Markets**. Under the traditional view of multi-market competition, when firms face each other in multiple markets, the cutting edge of competition is blunted and the rewards to more cooperative behavior increase. In their model of strategic behavior, "firms may find it profitable to redistribute market power across the markets, so that the total profit maximization can be achieved by giving up profits in less competitive

markets in order to increase profits in more competitive markets." They hypothesize this would compress price differences across markets. Using IMS Health data from 1998 to 2003, they find preliminary evidence supporting this in countries with more liberal markets (US, Canada, Germany and the UK), but not in highly regulated markets (France, Italy and Japan). They conclude that multi-market contact between firms may be inducing strategic behavior.

Peter Sheehan and colleagues at Victoria University focus on how the Australian health system rewards firms for innovation - noting that it is the total revenue, not price, which is a firm's reward. Their preliminary analysis focuses on price and volume indices for drugs that entered the Australian market since 1992. For each cohort (based on year of entry) they found a consistent pattern. After the initial product launch, there were significant price decreases early in the patent period indicating that "any return to innovation in original price (set after cost-effectiveness analysis) quickly eroded." In looking at the effects of generic entry, they found that given these observed price reductions, generics had a limited impact on either price or volume. In Australia, generics are about 21% of the volume as compared to nearly 50% in the US. From these analyses they conclude that although "returns to innovation through prices appear to be low, sustained volume effects may be some offset."

Antonio Cabrales and colleagues at University Pompeu Fabra de Barcelona presented their paper, **Generics, Product Differentiation and Policy**, which develops a game theoretic model of vertical product differentiation to explain four fundamental observations about the impact of generic competition across countries. These observations are:

- Countries with lower prices for branded drugs typically have lower generic shares.
- Countries with more regulation tend to have a lower impact of generics.
- The affects of generic competition on branded drug prices are ambiguous.
- Countries with increased regulation seem to have lower rates of innovation.

In their model, consumers agree on the quality differences, but disagree on their willingness to pay for those differences. This leads to a situation

in which, after generic entry, it is optimal for the higher quality branded product to actually increase its price, relative to when it was on patent. Moreover, the lower the price ceiling (set by the regulator) the higher the resulting share of the branded products, and the less incentive for generic products to enter the market. For these results to hold, they need either large R&D or marketing budgets with decreasing returns to scale. Their next steps are to develop empirical validation for their model.

Panos Kanavos and colleagues at the London School of Economics are beginning an econometric analysis of the demand for cholesterol-lowering statin drugs, using data from the UK, France, Germany and the Netherlands for the time period 1992 to 2002. Their paper, *Competition in Pharmaceutical Markets*, included a country-by-country analysis, focusing on the market share of the first entrant. They plan to extend their analysis by looking at the effects of regulatory interventions and by employing more powerful panel data techniques. In a second analysis, they examined generic entry in the ACE market and found that the volume of branded sales dropped significantly across all markets after generic entry. The effects on price, however, varied by country. In the Netherlands and Germany, the prices of the branded products fell significantly after entry (perhaps because of regulatory constraints) while in France and the UK prices remained at current levels or perhaps even increased.

Juan Rafael Vargas and his colleagues at the University of Costa Rica have been studying *Regional Prices Discrimination: Drugs in Central America*. They focused on the prices wholesalers charged retail outlets in four Central American countries, Costa Rica, El Salvador, Guatemala, and Nicaragua. These countries provide an interesting case study of how prices vary across markets: not only does Gross Domestic Product (GDP) per capita vary seven-fold across these countries, but government expenditures on healthcare also vary significantly. Using IMS Health data on wholesaler prices, they concluded that “the marketing strategy of the wholesalers in Central America comes out clearly from the empirical work. It is to sell the same drugs at higher prices in El Salvador and Guatemala relative to Costa Rican prices. In Nicaragua drugs are sold at substantially lower price.” In subsequent research, they examined data on 79 medications from 20 retail outlets in San Jose and Cartago and discovered that price differences as great as 20% were found across

these retail outlets. They concluded that “price differences are structural and could be explained by drugstore's location (local market power), characteristics (differentiation from competitors), market segment, and on the existence of search costs by consumers.”

Competition occurs at many levels. It occurs in the development of new products. It occurs in the sales and marketing efforts of the manufacturers. It occurs at the wholesale level, and even at the retail level, as Vargas showed. Given this vigorous competition and segmented markets, average prices will vary from country to country^{9,10}. Developing a better understanding of the competitive forces at work in these different levels is an important component of many of the PPPI program participants' research agendas. Ongoing research is already providing insights at both the theoretical level (Marin, Cabrales) and at the empirical level (Sheehan, Kanavos, Vargas). This work is helping to create a better understanding of the market forces at work in this complex industry.

⁹ Danzon, P., Furukawa, M. “Prices and Availability of Pharmaceuticals: Evidence from Nine Countries”. W3.521 (2003). *Health Affairs Web Exclusive*. http://content.healthaffairs.org/cgi/content/full/hlthaff.w3.521v1/DC1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=danzon+&fulltext=prices+and+availability+of+pharmaceuticals&andorexactfulltext=and&searchid=1093886556684_1673&stored_search=&FIRSTINDEX=0&resourcetype=1&journalcode=healthaff

¹⁰ Danzon, P., Towse, A. “Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents”. *International Journal of Health Care Finance and Economics* 3 (2003):183-205.

Observations and Conclusions

One important feature of the PPPI meeting was the opportunity for lively discussion among the participants. These discussions often strayed into interesting territory beyond the bounds of the formal presentations. What follows is a summary of key themes drawn from those discussions.

- A recurring theme was **the search for a unified theory to integrate the issues of pharmaceutical policy into the broader domains of health, social, trade and industrial policy** (including the role of government). On the one hand, government is often a major purchaser of pharmaceuticals, and therefore is interested in reducing costs. On the other hand, pharmaceuticals also help improve the health and productivity of the population. And finally, in some countries, the pharmaceutical industry is a potential source of economic growth and international trade. The goal is to achieve the right balance between sponsoring an environment conducive to innovation (supporting high standards of intellectual property protection, university science programs, basic research, transparent, efficient and predictable regulatory systems, entrepreneurial activity, and venture capital markets) and ensuring that citizens have access to appropriate medicines at affordable prices. Another difficult balance governments seek is that between educating citizens about the availability of treatments and protecting them from misleading or false information that plays against their fears of disease and illness. It is clear that some countries lean in the direction of supporting economic growth and free markets, while others are more protective and focus on equity and social solidarity. These choices seem to reflect basic differences in societal values.
- Another theme centered on **what criteria should be used to evaluate these policies**. Before one can answer “What is best for society?” one must first determine which society one is most concerned with (local, national, or global). The question of perspective is crucial for the pharmaceutical industry, because pharmaceutical R&D results in knowledge that is a global public good. With public goods there are often large distributional issues and free

riding is a major challenge. Under the current system, intellectual property rights are used to provide the protection that enables private innovators to reap the rewards of their efforts. At the same time, governments often impose restrictions on pricing and reimbursement to guard the interests of their citizens and taxpayers. When making recommendations on policy issues, how should one balance the national interest with the supra-national interests?

- Underlying much of the discussion was the issue of the extent to which distributional concerns matter — that is, **does it matter who gains and who loses?** In pharmaceutical policy, economists tend to focus on the issue of efficiency, and try to promote policies that “maximize the size of the pie.” In this context, one can look at it from a global perspective and focus on making the maximum use of the available technologies. Unfortunately, in the real world the equity and distributional effects can be quite important. There are often winners and losers from the adoption of specific policies, and frequently governments are led to act in the interest of their own citizens at the potential expense of other country’s citizens. Thus there was some movement in the direction of encouraging academics and governments to transcend their own nationalistic interests and focus more on the broader global issues.
- Any discussion about pharmaceutical industry issues would be incomplete without addressing **international price differences and the sustainability of the current pricing model** of market-based prices in the United States, and lower, regulated prices in much of the rest of the developed world. Considerable debate ensued as to whether the existing pricing system is fair, and whether US citizens are paying too much, and/or whether citizens of other countries were “free- or cheap-riding.” A central question is how fairness should be evaluated. Should one be looking at this in the context of absolute prices, prices relative to GDP per capita, or considering these questions in the context of total expenditures on pharmaceuticals? No real consensus emerged, other than an agreement that this is a polarizing political issue and that the current rhetoric is long on demagoguery but short on facts and data.

- A corollary to the discussion of prices was a more detailed discussion of how much the industry is **spending on product promotion**, and whether these efforts provide any benefit to consumers or, as some observers contend, simply push up the costs of medicines. It is frequently cited that if the industry spent less on promotion, then it could charge lower prices and still earn a reasonable return on its investment. Alan Mathios' work seems to suggest not only that the ability to advertise can stimulate additional innovation, but that it can also be vital in helping consumers change their behaviors in ways to improve their health. Clearly additional research is needed on this topic before one can confidently assess the impact of DTC advertising on health outcomes.
- There was much discussion about **the role of technical change**. In some countries it appears as if the governments believe that the primary role of technical change is to reduce costs — and they will only approve new technologies after a clear demonstration that their implementation can reduce total expenditures on healthcare. In other countries, governments appear to be willing to allow expenditures to rise if there is sufficient evidence of an improvement in the quality of care. A primary mechanism for assessing these characteristics is the use of cost-effectiveness or cost-utility analysis. These analyses attempt to assess the cost of additional improvements in patient outcomes, and after comparing to specific benchmarks, make a determination as to whether or not it represents value for money.
- **What does “access to medicines” really mean?** Does it mean having a drug on the pharmacy shelf, or in the medicine cabinet? The crux of the question is the role affordability plays, and the presumed trade-off between innovation and prices. But does there need to be a trade-off? Peter Sheehan's work reminded the group that price alone does not determine the reward to innovation, but rather total revenues over time. Are there policy solutions that allow for sufficient returns without requiring high prices? Can policy makers affect the volume and life cycle of products in ways that encourage greater innovation at lower prices?
- A final topic that received considerable attention was **how to increase the impact of the body of work done through the PPPI program?** Several issues were raised. First, timing. Policy makers tend to focus on a few issues at a time, and then move on. If academic thought leaders want to have more influence on policy decisions, they need to develop a closer feel for the issues of the day and come forward with their ideas at the appropriate time. Second, brevity. Policy makers tend to be very busy and pulled in many directions. Rather than producing dense tomes, it is often more effective to develop more succinct policy briefs that outline the central point of the analysis or model. If interested, the policy maker (or his or her staff) can always refer to the original source of information — but if the presentation is not concise, they won't have the time to read the information. And finally, there was agreement that it was important to engage policy makers early on in a research project. This can be done by beginning with a needs assessment to understand the kinds of information the government needs to help it in making decisions. Understanding what information is needed, and then providing it in a timely manner, is the best way to have a positive influence on the policy debate.

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PPPI Centers

Victoria University, Australia

<http://www.cfses.com/>

The mission of the Centre for Strategic Economic Studies is to: address long-term, strategic economic and social issues of international concern; consider the role and relationship of both general ideas and specific institutions; develop a specific focus on basic issues relevant to Australia's future, with special reference to the Asian region; develop and train a body of graduate students with the motivation and skills to address these strategic issues in the future. In fulfilling this mission the Centre pursues activities in three main areas: research on long term economic, social and technological issues; commercial activities, including publications, conferences and electronic data services; and postgraduate teaching.

Institute for Health Economics, Canada

<http://www.ihe.ab.ca/>

The Institute of Health Economics (IHE) is an independent, not-for-profit organization whose mission is to deliver outstanding health economics, health outcomes and health policy research and related services. The structure and approach to research at the IHE is unique. The Institute operates on the belief that in order for research to be relevant, all the players must be at the table; therefore, members of the IHE include academia, government and industry.

Fu Dan University, China

The program seeks to reach health targets through triple system reform in China. Researchers are studying urban medical insurance reform, health system reform and pharmaceutical distribution system reform. Health is a precious asset. Improving the health status of Chinese population is the final expected outcome of the reform and it requires multi-sector efforts.

University of Costa Rica, Costa Rica

The program places significant emphasis on training and research in health economics in the Latin America. As a result, they have the largest research output in the region and have graduated over forty students from a variety of disciplines including medicine, pharmacy, nursing, statistics and public administration.

University of Siena, Italy

<http://www.epris.it/>

The main objective of EPRIS is to develop a comprehensive analysis of the structure and evolution of the European Pharmaceutical Regulation and Innovation Systems. Emphasis is given to the cross-national/comparative aspects of industry structure and evolution, differences in health care systems, diversity in tradition of university-industry relationships, and the divergent growth rates of small biotech/drug discovery companies in US vs. Europe.

University Pompeu Fabra de Barcelona/ University Carlos III de Madrid Consortium, Spain

http://www.upf.es/cres/angles/index_eng.html (Pompeu Fabra)

<http://www.eco.uc3m.es/> (Carlos III de Madrid)

The Consortium is committed to academic excellence and research in the areas of health economics and health services management. In a recent comparison of economics departments, sponsored by the European Economic Association, Carlos III de Madrid was ranked number 51 in the world, number 10 in Europe, and number 1 in Spain. The

Economics and Health Research Center (CRES) is a special research center of University Pompeu Fabra. Their objective is to develop different analysis paths of the health care system from the university research perspective. Their claim is to help the changing process of training and services management in subjects related to Health Economics and Health Services Administration.

London School of Economics, United Kingdom

<http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/>

LSE Health and Social Care is a research centre in the Department of Social Policy at the London School of Economics and Political Science. The Centre's fundamental mission is the production and dissemination of high quality research in health and social care. Bringing together a core team of researchers and academics, LSE Health & Social Care promotes and draws upon the multidisciplinary expertise of forty-five staff members, fifteen associated academics and a number of postgraduate students.

Columbia/Stanford Consortium, United States

<http://www.medinnovation.org/>

The Columbia-Stanford Consortium on Medical Innovation, established in 2002, is a multidisciplinary research and training program. The overall objectives of the Consortium are three-fold: 1) to train a new generation of policy-oriented researchers, 2) to conduct research projects that carefully analyze how historical, economic, institutional, and regulatory factors affect the rate and direction of innovation in medicine and 3) to disseminate these results in the health care arena. The Consortium is led by faculty in Medicine, Public Health, Public Policy, Business, Economics, Sociology and Education at Columbia and Stanford University.

Cornell University, United States

<http://www.humec.cornell.edu/units/pam/cpph/>

The program on Consumers, Pharmaceutical Policy and Health promotes research, education and the development of research capacity in selected areas of pharmaceutical policy. The primary research focus of the program is on the causes, consequences and performance of public policies toward the pharmaceuticals industry, with particular emphasis on the interaction of public policies and private decisions for health and consumer well-being.

Massachusetts Institute of Technology, United States

<http://web.mit.edu/pop/>

The Program on the Pharmaceutical Industry (POPI) was established in 1991 primarily to promote research and educational activities on issues related to competitiveness, performance and productivity in the pharmaceutical field. This multidisciplinary research program is led by faculty from the MIT Schools of Science, Engineering, Humanities and Social Sciences, and Management. Participating faculty and graduate students include those with expertise in the fields of biology, chemistry, chemical engineering, economics, medicine, and the management sciences.

The Wharton School, University of Pennsylvania, United States

<http://knowledge.wharton.upenn.edu/category.cfm?catid=6>

Wharton's Health Care Systems Department brings particular strengths in health economics and health management. Disciplines such as law, policy, ethics, and decision analysis are represented by the department's secondary appointments and by faculty who work at the University of Pennsylvania's schools of medicine and nursing. Adjunct faculty members are also drawn from health industry experts in the Philadelphia area.

About The Merck Company Foundation

The Merck Company Foundation is a United States-based, private charitable foundation. Established in 1957 by Merck & Co., Inc*, the Foundation is funded entirely by the Company and is Merck's chief source of funding support to qualified non-profit, charitable organizations. The Foundation advances the Company's philanthropic outreach around the world and helps meet important needs of our society. Such needs include improving health care worldwide, advancing biomedical and science education, and supporting the arts, social services, as well as civic, environmental and other charitable organizations.

Since its inception, The Merck Company Foundation has contributed more than US\$340 million to address critical global health, education, environmental and other societal needs.

Additional information about the PPPI can be found at www.merck.com/about/cr/pppi.

*Merck & Co., Inc. operates as Merck Sharp & Dohme (MSD) in most countries outside the United States.

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