

The Economics of Innovation: Global Price Controls and the Future of Biomedical R&D

On February 19, 2004, The California Healthcare Institute (CHI) convened a group of distinguished leaders who influence healthcare policy across the spectrum of industry, government, and academia to discuss price regulation in the global context. The discussions specifically focused upon the cost of innovation in the field of drugs, devices and related technology, and the ongoing struggle and ensuing tension that comes from balancing the cost of innovation with access to the latest advances. Industries represented included biotechnology, pharmaceuticals, medical devices, diagnostics, venture capital, academic research along with representatives from government who legislate and enact policy that affects these industries. Summarizing CHI's mission, David Gollaher, President and CEO of CHI, explained, "CHI endeavors to bring together the people who are the most influential and the most responsible for the public policy that affects our collective industries... with the people who run those industries, who, in fact, are the industry." This white paper captures the highlights of the discussions held at the Keck Graduate Institute of Applied Life Sciences that day and sets forth a record of the key issues under debate as identified by members of CHI.

PRICE CONTROLS KILL

Congressman David Dreier, Chairman of the Rules Committee in the U.S. House of Representatives, believes that there is a notion afoot that many people have been pursuing at a grassroots level in regard to healthcare in general, and to drugs in particular—the notion that one can get something for nothing. That notion, he warns, is misplaced. The current demand for drug re-importation as a means to price control is fast becoming the grassroots cause du jour. Dreier stated his position in plain terms: "To me, what re-importation really is, it's the importation of a command-and-control economy, which is antithetical to everything that we stand for." Dreier maintains that while there is, in fact, a cost to be paid for quality healthcare, there is also a tremendous reward. The reward is nothing less than the opportunity to improve—if not save—lives.

"I'm talking about the issue of re-importation; I'm talking about this whole notion that so many people have been pursuing, that you obviously can get something for nothing." —David Dreier

James K. Glassman, resident scholar at the American Enterprise Institute, also sees the issue of price controls as being a matter of life and death. And when it comes to the cost of an extra year of life, for which the current research assigns a price tag of \$4,500, the price seems reasonable. In the end, he asks, who gets to say whether prices are too high or too low?

Glassman answers his own question by framing the discussion in the most basic terms of supply and demand. He outlines the problem in U.S. healthcare by stating that supply is constricted and demand is enormous. The supply of drugs is restricted largely because it is so expensive to bring a new drug to market; demand is tremendous because people want to live longer—and better—lives. It's a hard thing to come to terms with, Glassman concedes, but if people want to live longer and healthier, they need to pay for that privilege.

Illustrating this point, Glassman cited a study presented at the World Economic Forum in Davos, Switzerland, on January 22, 2004. This study compared the United States with Germany

in regard to the health of the respective populations. Germans spend more time in hospitals, lose more working days to sickness, and those Germans who suffer from heart disease and breast cancer have higher mortality rates. Significantly, Germans have price controls and Americans do not. If re-importation happens, Americans will become less healthy. More Americans will die.

The most effective lever the healthcare industry has to ameliorate prices is the lever of supply. The least effective lever is that of price controls through re-importation or any legislative decree.

FREE RIDING ISN'T FREE

Increasing supply is dependent upon the industry's ability to bring new drugs to market, which in turn is dependent on a robust R&D pipeline; which, in its turn, is dependent upon obtaining sufficient capital to fund the R&D; which is, finally, dependent upon there being a sufficient return on the R&D investment to reward investors.

Speaking from the perspective of the investor, Drew Senyei, M.D., managing director and general manager of Enterprise Partners Venture Capital, sees the issue of Canadian re-importation as a lightning rod that points to disturbances within a complex ecosystem. This ecosystem is a result of what he calls a harmonic convergence of favorable government policies, such as the 1980 Bayh Dole Act, which provided support for the technology transfer process, along with leading-edge science and the muscle provided by the capital markets, all of which have enfolded over the past twenty-five years. Senyei credits the remarkably robust biotechnology industry today, which enjoys more than \$45 billion in sales and 155 marketed products, to these drivers. However, Senyei argues that the most critical factor in building the industry has been the U.S. free-market policy toward the pricing of innovative products. He points out that among the top fifteen drugs marketed in

the U.S. today, the majority came from U.S. innovations, whereas twenty years ago European countries dominated the field.

"We are the beneficiaries of what has been a harmonic convergence over the last twenty-five years of really favorable government policies, incredible science, and the ability of the capital markets to put capital to work to make these science projects effectively become reality." –Drew Senyei

Senyei points out that most of the innovation has come from small venture-backed biotech companies, citing as evidence the statistics for 2001: Two-thirds of the thirty-two biologics and NME's that were approved came from small biotech companies or had their origins in academic labs. What was a trickle of funding in the late '70s and early '80s has become a torrent of funding with more than \$100 billion going into the venture industry in 2000.

Mark McClellan, M.D., Ph.D., Administrator for the Centers for Medicare and Medicaid Services and former Commissioner of the Food and Drug Administration, acknowledges that private investment currently provides approximately two times the research capital that NIH does.¹ Through private investment combined with the doubling of the NIH budget, there is a tremendous amount of R&D going on. Yet patients are not yet benefiting from that investment. As McClellan stated, "We're at an absolutely critical time when there are a lot of good ideas in the pipeline, but unless you... bring those ideas to patients, and unless there is a reward at the end of that pipeline to make sure that the investment keeps coming, we may not see the real benefits of these truly innovative developments in modern biomedical sciences... And that's why being involved in health policy, whether it's the Rules Committee or at the FDA or elsewhere in government, is so important today."

¹ Dr. McClellan was confirmed as Administrator for the Centers for Medicare and Medicaid Services on March 12, 2004. At the time of the Keck Graduate Institute discussions recorded in this white paper he was Commissioner of the FDA.

Now, for the first time, the life sciences sector is receiving the largest proportion of venture dollars of any category; the only other category to even come close to its level is software. Both McClellan and Senyei agree that to keep this trend going it is important for the U.S. to maintain our current competitive position. Companies have to provide incentives for investing in these risky, long-term projects by offering investors commensurate rewards. If they fail to provide rewards, they will lose the ability to attract capital to fund their innovations.

“We’re at an absolutely critical time...”

–Mark McClellan

Senyei puts a number to the level of rewards venture capitalists require. “For early-stage investors like myself, [the returns] must represent a four-times or greater multiple over a five- to eight-year period or a 25-35% IRR.” Senyei insists, “We must also maintain the ecology, this harmonic convergence of events that has made all this possible, and that includes maintaining the intellectual property laws, continuing to improve the FDA that [former] Commissioner McClellan has led so ably, and we must also continue to reward the entrepreneurs by free-market pricing; otherwise, they will not continue to innovate.”

McClellan agrees that it is Americans who, through the higher prices they pay for drugs, are funding a disproportionate share of the research cost that goes into the many years of development required to bring safe and effective new medicines to the world’s citizens. Indeed, Americans are shouldering a burden that should be more equitably distributed.

At the same time, McClellan acknowledges that many Americans are rightly worried that drugs in development today may not benefit them if they can’t afford them once they come to market. Furthermore, not only are Americans worried, they are downright angry about the cost of drugs,

especially when they see companies marketing the same drugs in other countries with price-controls, such as Canada, at a fraction of the cost.

Susan Desmond-Hellmann, M.D., M.P.H., Executive VP of Development and Product Operations and CMO of Genentech, has a similar perspective. “I think that at the heart of the issue of re-importation is the larger, more important fact that high-income countries have put in place an anti-market pharmaceutical regimen that puts the cost of research and development for new drug therapies squarely on the back of American consumers...What makes me angry is that we’re paying the cost of R&D for the world. And I think that’s not okay.” The logical conclusion of this state of affairs, she explains, is that if Americans join the free riders who don’t want to pay the cost of development, then nobody will be paying for the R&D needed to develop new therapies, so there’ll be fewer cures in the future.

“Innovation for me is no more and no less than thinking we can do something better for patients.” –Susan Desmond-Hellmann

Desmond-Hellmann’s arguments for innovation come directly from her experience as a clinician. As she puts it, “I’m not a politician; I’m not an economist. The contribution I can make...is to talk about what innovation means for patients and why I care a lot about spending money on R&D.” To illustrate her position, Desmond-Hellmann points to the story of the development of a breakthrough product, Avastin, a new anti-angiogenic product for the treatment of colon cancer.

Desmond-Hellmann’s story begins with Dr. Judah Folkman’s great pioneering work, which first came to her attention with the publication of his article on anti-angiogenesis in the treatment of cancer in the *New England Journal of Medicine* in 1971. Folkman’s idea was that instead of killing a cancer cell through the administration of poisons via chemotherapy, the cancer could be arrested by starving it of the

blood supply that fed the tumor. Ten years later in 1981, after much controversy, his idea was validated, and along came the discovery of the vascular endothelial growth factor, or VEGF, as the key signal used by oxygen-hungry cells to promote growth of blood vessels. More than 15 years later, in 1997, Genentech filed the IND with the FDA to start the clinical trials on anti-VEGF, or Avastin, in order to develop a drug that would utilize this knowledge. Now, seven years later, on February 26, 2004, Genentech received approval of Avastin for patients with metastatic colorectal cancer. With this approval comes hope for the 69,000 people in the United States who are diagnosed with colorectal cancer, a type of cancer that spreads and can't be cured. For these 69,000 people there is now hope for longer life. Desmond-Hellmann's story ends with a reminder that this breakthrough was almost thirty-five years in the making, and that a development timeline of this length is not at all unusual in the world of drug development.

Desmond-Hellmann warns that the ability to tap into the science that is currently cutting-edge—proteomics, genomics and nanotechnologies, to name a few—won't occur if the industry doesn't have the tenacity to continue scientific explorations fueled by the kind of investment resources that can sustain projects that don't yield immediately marketable outcomes. Desmond-Hellmann sums up her perspective with the words, "Innovation for me is no more and no less than thinking we can do something better for patients." Price controls are simply not compatible with doing the best for our patients.

Further complicating matters, free riding through price controls carries hidden costs to both patients and to their countries' economies. The Bain study released at Davos in January has powerful data that argue against price controls. Glassman highlights the findings, "While Germany saves \$19 billion in drug costs through price controls, its loses \$22 billion due to reduced R&D, bad health outcomes, and the loss of high value-added jobs."

CHANGE MINDS IN EUROPE AND IN CANADA

Where do we begin to try to right the imbalance that exists in global pricing? Glassman suggests that a good place to start is by trying to change the mindset of Europeans and Canadians. He points out that human beings are actually suffering in Europe and Canada as a result of their countries' government-controlled healthcare systems, and directing arguments to those who suffer is a good idea. As their understanding deepens, their minds will change, and as their minds change they can help bring about economic and political change.

Glassman influences these mindsets by writing position pieces in the *Wall Street Journal Europe* and the *Globe and Mail* in Canada.

For his part, McClellan encourages industry leaders and policy makers to make a more conscious effort to encourage all nations to work together to provide fair incentives for developing valuable new medicines. If we don't do this, he warns, we aren't going to see the improvements in health that benefit everyone around the globe. He believes that other nations don't necessarily need to increase their overall spending; they just need to reallocate their pricing. In Canada, the U.K. and France, for example, the cost of many generic drugs is markedly higher than in the United States and patient access more severely restricted. If the prices of European generic drugs were adjusted, their availability increased and the surplus money was plowed back into better investment, the issue becomes less about spending more and instead about getting more for what is spent.

In the meantime, McClellan has very definite opinions about the issue of drug re-importation, and, in particular, Canadian re-importation. He firmly believes that under our current regulatory authorities and resources, including the FDA today, importation cannot be done safely on a large scale.

McClellan illustrates his concern by citing an example based on recent findings from the state of Minnesota. Minnesota pharmacy regulators

visited Canada to explore a cooperative relationship between Canadian Internet pharmacies and drug wholesalers. Their intent was to visit these drug outlets and to review their standards in comparison with the set of standards established for safe practices in the U.S. Only eight Canadian companies chose to invite the Minnesotans to visit, and of the eight only one Canadian company was found to comply with U.S. standards. Regulators reported dangerous practices included unsupervised technicians dispensing drugs, poor storage practices such as the lack of proper refrigeration, unsafe labeling and improper shipping.

McClellan is aware of other significant safety gaps that exist in the Canadian drug distribution system, such as the lack of a workable means to administer drug recalls, the practice of distribution companies accepting drug order faxes directly from patients, and the basic lack of supply to serve a large-scale solution.

Despite these very real safety issues, McClellan recognizes that there is real momentum gathering in Congress behind legislation sanctioning importation. In fact, the Medicare legislation passed last year directed the FDA to take a serious look at what would be required to import drugs into this country safely including new authorities, among other resources. The FDA's report is due this December. Given this deadline, McClellan urges the industry to step forward to proactively engage other countries in alternative solutions to importation. To protect the investment associated with innovation and ensure that products now in the pipeline can come to market, real steps must be taken in short order.

"It's important for countries to accept what is fair pricing, and we've been able through hard work to achieve that... it seems that there's light at the end of the tunnel." –John C. Martin

While skeptics dismiss the likelihood of a fair pricing resolution coming about through global

cooperation, there are companies making significant progress. One of those companies is Gilead Sciences. Gilead has six products on the market today, all of which were released in the past ten years. These products address a variety of important medical needs; they range from providing a life-saving antidote to severe fungal infections, to a pill for the treatment of all strains of influenza, to a treatment for hepatitis B, to two very potent anti-AIDS drugs that are currently being combined into a single-dosage pill to further simplify therapy for AIDS patients.

As a company with a strong presence in the treatment of HIV/AIDS, Gilead has stepped into the forefront of what's going on in terms of drug access around the world, which in turn has provided a firsthand view into the relationships that now exist between worldwide access and pricing. John C. Martin, Ph.D., and President and CEO explains, "It's important for countries to accept what is fair pricing, and we've been able through hard work to achieve that... it seems that there's light at the end of the tunnel."

The fact is, Gilead has adopted a policy of working very hard on global pricing strategies on an ongoing basis. They believe that there should be tiered pricing relative to countries' abilities to pay. In addition, the pricing also needs to reflect the innovation cost while at the same time remaining competitive within the price bands established by similar drugs on the market. Martin reports that within Europe Gilead now has a range of prices that are in a fairly tight band based on each country's ability to pay. He adds that negotiating these prices was difficult with some of the negotiations taking more than a year to conclude. However, Martin points out that Gilead's persistence has paid off, and in the end, the European prices they negotiated were very similar to the U.S. prices. "We proved we can do it," Martin remarked. "Over time a gap may develop, but at least now, at this point in time, we're where we want to be."

Meanwhile, despite the issues of re-importation and price controls, Canada remains an

attractive market to many U.S. companies. Gilead's experience in Canada shows that there are strategies that will allow a U.S. company to launch a drug in the Canadian market while preserving pricing that is comparable to the domestic market.

Gilead launched an expanded access program for their AIDS drug, Viread, at the time they received approval for Viread in the U.S. Then, over a period of two and a half years, they negotiated Canadian pricing that was reasonably comparable with their U.S. price. During this negotiation period, they had 10% of the patient population in Canada enrolled in their expanded access program, which meant those patients were receiving Viread free of cost.

Martin admits the free access program was the price Gilead had to pay for entering into a longer-term price negotiation that established the Canadian price prior to launching the product. While this strategy worked out reasonably well, Martin looks forward to a time when it will be less challenging to work through their system. As he puts it, "We'd like to see the Canadian system improved somewhat just as everyone else would, but I can say that it seems that there's light at the end of the tunnel, and I think it may well be because of the can-do attitude of people like Chairman Dreier and Commissioner McClellan."

FREE RIDING IS IMMORAL

Americans would agree that it's okay if the third world gets a free ride. We all understand the need to provide compassionate care in these countries. It is not okay, however, if developed countries such as Germany and France free ride. This is very serious; it's immoral and it's an unsustainable model.

Gilead offers a model of how to balance compassionate care for the third world while fostering economic parity among developed nations. Gilead makes drugs available prior to approval where appropriate by way of a compassionate or expanded access program. Although it is expensive to not only give away the drug for free, but

also to cover the enrollment costs of the associated clinical studies, this policy has been enacted in many countries of the world. The enrollment costs run up to \$2,000 per individual, but it's worth it. As Martin explains, "With the types of drugs we're working on, in many cases patients are too sick to wait for the approval. And so it's important to make it available."

Gilead also aggressively supports programs in the developing world. They work with a variety of organizations to make sure that their drugs are available in countries such as Africa at the manufacturing cost. These programs are seen as pure philanthropy without any attempt to recover even the cost of goods. Gilead has also established middle-tier pricing that makes sense in certain developing countries such as those in Latin America. All these programs have been effective and will continue to work so long as the developed countries recognize that if the U.S. pharmaceutical industry is going to provide drugs at cost, these drugs can't flow back into developed nations as deeply discounted products. Martin is firm on this point. "That's simply not going to work. And one of the things we were particularly pleased about last year is, we were able to work with the FDA in an expeditious way to actually change the color of our pill for Africa and the other fifteen least-developed countries we're providing it to at cost." This simple solution provides a way to differentiate drugs targeted for needy countries in a way that makes re-importation unlikely.

PRICE CONTROLS NEVER WORK

To understand why price controls never work, we must go back to the laws of supply and demand. Glassman is a firm advocate of this line of reasoning. As he says, "When you set a low price, you reduce supply, which puts further upward tension on prices, increasing the gap between the control price and what we could call the natural price, the price where the supply and demand lines are supposed to cross. When this happens governments have to reduce demand through triage, which means they refuse to allow people

to have life-saving or life-enhancing drugs and devices. For example, 30% of the diabetes patients in Germany are not treated with drugs at all. In France, only 50% of patients with multiple sclerosis who are eligible for treatment with beta interferons actually receive it. This occurs today throughout Europe.”

McClellan warns industry leaders that when they comply with foreign price controls, they are effectively sanctioning these artificially low prices. This only contributes to the mounting anger here in the United States.

“We need to try a different approach.”

—Mark McClellan

Professor Alan M. Garber, M.D., Ph.D., Stanford University, recognizes the urgency in the current situation Commissioner McClellan outlines. “The anger that Mark refers to is very real... Members of the public are very angry that the Canadians and worse than that, the French and the Germans—pay less for their drugs than Americans do.”

EDUCATE THE PUBLIC

Congressman Dreier suggests that the best way to combat the grassroots demand for lower prices is to educate the United States public about the challenges the industry is facing and the benefits they receive for the prices they pay.

“You are in trouble—the threats to innovation are real.” —James K. Glassman

Glassman offers a Washington perspective, “I come from Washington, and I have a very simple message today, which is that you are in trouble... the threats to innovation are real. They are growing. And they are led by demagogues who are making inaccurate and unprincipled arguments, either disingenuously or ignorantly. I can’t quite tell the difference.” Whatever their motives may be, the fact is, the public is listening.

In a recent debate held in San Francisco between Congressman Gil Gutknecht from Min-

nesota and Nobel laureate economist Milton Friedman, Glassman reports that while Friedman spoke of supply and demand, the Congressman had the crowd-pleasing arguments for price controls down to a tee. Glassman suggests that in order to counter these emotion-laden public displays the industry is going to need strong ammunition in its fight. It becomes especially challenging, he adds, when the legislators who are backing price regulations and drug re-importation are being assisted in their message by the popular media. To illustrate his point, Glassman referred to the February 2, 2004, *Time* magazine cover story entitled “Why We Pay So Much for Drugs,” as only one example of many where the media reinforces the image of drug-makers as greedy companies with little or no interest in public welfare rather than acknowledging them as the innovators they truly are.

Glassman gave an approving nod to former Commissioner McClellan, who, he said, has been holding the line on re-importation. But Glassman is yet another expert who doesn’t think that an argument against re-importation based upon safety is going to win the day in the long run.

One trend the public should be aware of is the major steps that are being taken in the United States toward ensuring that when legitimate patents expire, the field is open for widespread generic competition. Although the public may not realize it, the U.S. prices for generic drugs are already among the lowest in the world. Generic U.S. medicines for diabetes, anxiety, heart disease and blood pressure are on average 40% less than in Canada. In addition, generic drugs are widely used in the United States, totaling about 55% of prescriptions last year. That ratio will likely increase in the coming years as more blockbuster drugs come off patent.

McClellan argues that we should not endorse policies that reward companies for bringing a drug to market and then milking it for several decades. Unfortunately, this is what happens if you drive down the price of new drugs and drive up the cost of generics—a pricing model that is

common in Europe. That kind of pricing structure takes away the incentive to innovate. Rather, governments should encourage competition in generics and allow the price of new patents to more fairly reflect their investment cost.

Garber takes a different tack when he encourages the industry to think about the issue of pricing from the point of view of the payer. The issue of high drug prices then comes across not so much as an issue of the greed of the pharmaceutical industry or the lack of price controls, instead it reveals itself as a function of an historical market where third-party payers —commercial insurers, for example —paid most, if not all, of the costs of any services covered by insurance. With this system we created a monopoly selling to people who were not really paying for what they were consuming.

By way of illustration, Garber compares the pharmaceutical industry to the airline industry. He asks, who minds if they're paying five times the price their seatmate is, as long as their company is footing the bill? But if the passenger suddenly has to pay 20% or 30% or 50% of their travel expenses, they're going to speak up and demand that they pay no more than the next guy. Similarly, as the insurance companies pay less in benefits, and healthcare costs more out of pocket in both relative and absolute terms, Americans question pricing that was acceptable when someone else footed the bill. To make matters worse, many of the new medicines provide benefits that people simply don't want to live without. Opting out of treatment to save money has significant consequences and is not an acceptable solution to the public. Given the complexity of these issues, the need for public education is urgent.

MAKE COMMON CAUSE WITH OTHER INNOVATIVE INDUSTRIES

In offering a solution to the healthcare industry, Garber questions the administration and industry's struggle over re-importation. He believes that this struggle is essentially a rear-guard action because the most successful outcome would be,

presumably, a blockage of re-importation. Garber differs somewhat from his colleagues in saying that he would not recommend that the administration hold their trade policy hostage to this one issue. Instead, he challenges the healthcare industry to exert its market power in order to change how it sells overseas. He recommends letting market demand for critical products drive pricing, arguing that if companies don't push their margins to the fullest, they can't expect government to step in to solve their problems.

"This healthcare market is a very strange market." —Alan M. Garber

Glassman, meanwhile, recommends that while the industry flexes its muscles to attain appropriate pricing, it should also join forces with other industries that are under attack from protectionists or those who want to import price controls into this country.

Garber poses the ultimate question for consideration: "What would you, the industry, like the healthcare system to be? Do you want it to be something like a single-payer system in which you use political influence as your primary instrument to get adequate reimbursement, or do you want it to be something that's more competitive? And if you want it to be something that's more competitive—something, say, involving plan choice—that means you need to allow the plans to exert their market power to try and get low prices and to shift people's utilization toward cheaper drugs as they see appropriate... The point is, very simply, you cannot solve this problem of price controls and re-importation in isolation. It's a symptom of a larger problem, and I would suspect that it won't be solved until we have a very meaningful dialogue in the broader context of change in healthcare markets."

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