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The Re-Structurings of Global Pharmaceuticals: An Historical Perspective on the Interactions of Science, Markets, Public Policy and Patterns of Innovation

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In the past century public health in the developed nations has been transformed by improvements in physical infrastructure (water and sanitation); by public and private investments in health care facilities, in training health professionals, and in health insurance schemes to ensure that people have access to care and treatment; by prevention and health promotion; and by the products of pharmaceutical innovation. Since World War II in particular, the pharmaceutical industries in a small number of nations have harnessed the forces of innovation, markets and public policy to create business models that have been singularly successful in addressing the medical needs of the developed world.[1] In the recent period of dynamic change, the pharmaceutical models have combined heavy investments in research and development, in marketing and sales, in

[1] For a recent assessment of the impact of drugs on mortality see Frank R. Lichtenberg, "Pharmaceutical Innovation as a Process of Creative Destruction," in Mariana Mazzucato and Giovanni Dosi, eds., *Knowledge Accumulation and Industry Evolution: The Case of Pharma-Biotech* (Cambridge, 2006), 21-72: "We found that, in both of the two periods we studied (1970-80 and 1980-91), there was a highly significant positive relationship across diseases between the increase in mean age at death (which is closely related to life expectancy) and the share of new 'priority' drugs in total drugs prescribed by doctors…. [These figures] also imply that innovation has increased life expectancy, and lifetime income, by about 0.75 to 1.0 percent per annum…" (p. 69).

manufacturing, and in clinical operations oriented to well-developed Western systems of regulation.

During the years since 1945, the pharmaceutical industries have been significant drivers of economic growth. The life sciences have played an important role in the economic performance of the developed nations and have recently become substantial components in the industrial policies of some of the leading developing countries. The aspirations of these emerging economies are currently just beginning to affect the structure and performance of the global industry, but they will certainly have even more impact in coming decades. That future, we believe, will be conditioned by complex interactions of science, markets, and public policy – just the sort of interactions that have dominated the industry's evolution in the past.[2]

Our central concern is the manner in which the modern pharmaceutical innovation model has shown increasing signs of strain during the past two decades. Since we are interested in the sources of this strain, we examine both the external and internal factors that are stressing what for many years was an unusually successful model. The transformation we are examining is still very much underway. So our observations are preliminary and exploratory.

If we were dealing with an industry in transportation or manufacturing, we might simply proclaim that this is a "mature" industry, with the slower growth rate in demand, declines in innovation, and falling rates of profit that one frequently finds in older industries. But this is clearly not the case with pharmaceuticals. The aging of world populations, combined with increases in longevity, indicate that the markets for

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[2] We have thus situated this article in what Franco Malerba and Luigi Orsenigo, "The Dynamics and Evolution of Industries," *Industrial and Corporate Change*, 5 (1996), 51-87, identify as the third level of historical analysis.

pharmaceuticals will continue to increase over the long-term. Moreover, the demographic transitions in developing countries will leave them faced with growing burdens of diabetes, asthma, cardiovascular disease, cancer and other conditions that have traditionally been of major concern in more affluent populations. Demand is continuing to increase. So we need to dig a bit deeper than that.

The best place to start, we believe, is by sketching an historical framework focused on the rise and fall of the previous innovation models in this industry. Fortunately, we can draw upon the work of the many outstanding scholars who have examined pharmaceutical history in the nineteenth and twentieth centuries. They provide us with carefully documented analyses of the shifts that have taken place in global markets, the major changes in patterns of use of pharmaceuticals and vaccines, and the fluctuations that have taken place in the productivity of the current and previous innovation models. They have charted, as well, the recent rise of a vibrant biotechnology sector and analyzed the impact of public pricing policies in the past and present. To begin, we need to consider some of excellent analyses of the German innovation model.

The German Innovation Model

In the second half of the nineteenth century, the German model became the dominant paradigm in pharmaceutical innovation. It enabled German producers to quickly overcome the British industry and then to remain dominant for the next century.[3] While the British chemical industry was well established, its science base was in traditional products, largely for industrial use, and the firms devoted very few resources

[3] Johann Peter Murmann, *Knowledge and Competitive Advantage: The Coevolution of Firms, Technology and National Institutions* (Cambridge, 2003), 32-93. See also John J. Beer, *The Emergence of the German Chemical Dye Industry* (Urbana, 1959).

to research.[4] In these decades, the leading British universities were still emphasizing a classical curriculum that gave little heed to the modern sciences. From time-to-time, talented individuals rose above these constraints and produced important discoveries.[5] But lacking a system that could embed capabilities and sustain innovation, Britain's industry was rather quickly pushed out of the markets German firms were serving.[6]

The well-documented sources of German strength in pharmaceuticals included: the world's leading science base in organic chemistry; a large number of scientists who looked upon industrial research with favor; and governments inclined to support any enterprise that promised simultaneously to increase exports and best a leading British industry. National identity was becoming a potent force that justified policies – cartels for instance – that were very favorable to successful industries like pharmaceuticals. As the German industry developed, it sprinkled outposts and the German innovation model around the developed world. In Switzerland, there was a group of firms clustered in Basel, which became an important center for pharmaceutical innovation in 20th-century Europe. In the United States, Merck & Co., Inc., evolved out of a German distribution

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[4] Johann Peter Murmann and Ralph Landau, "On the Making of Competitive Advantage: The Development of the Chemical Industries of Britain and Germany Since 1850," in Ashish Arora, Ralph Landau, and Nathan Rosenberg, eds., *Chemicals and Long-Term Economic Growth: Insights from the Chemical Industry* (New York, 1998), 27-70; Christopher Kobrak, *National Cultures and International Competition: The Experience of Schering AG, 1851-1950* (Cambridge, 2002).

[5] See, for example, the accomplishments of William H. Perkin and his synthesis of dyes. Johann Peter Murmann, *Knowledge and Competitive Advantage*, Appendix I: A Technological History of Dyes," 237-57.

[6] There is now an extensive literature on organizational capabilities (as distinguished from individual accomplishments). See, for instance, David A. Hounshell, "Assets, Organizations, Strategies, and Traditions: Organizational Capabilities and Constraints in the Remaking of Ford Motor Company, 1946-1962," in Naomi R. Lamoreaux, Daniel M.G. Raff, and Peter Temin, "Learning by Doing in Markets, Firms, and Countries" (Chicago, 1999), 185-208, with a comment by Sidney G. Winter, 208-18. Alfred D. Chandler, Jr., "Organizational Capabilities and the Economic History of the Industrial Enterprise," *Journal of Economic Perspectives* 6, 3 (1992), 79-100.

center established in 1887 in New York City (for E. Merck of Darmstadt), with production facilities in New Jersey.[7]

Two world wars later, however, the German innovation model in pharmaceuticals gave way to a new American model. The wars and their aftermath were devastating to the German economy and society, but it is important to bear in mind that many of Germany's industries recovered very quickly – astonishingly so – after the war. But there was no German Miracle in pharmaceuticals. Why? We believe the primary factor was external to the industry and its leading firms. The postwar problems of higher education and professional training in West Germany weakened the industry's science base. This happened just as the need for adaptive change was increasing as the long cycle of organic-chemistry-based innovation was coming to an end. No longer were German research institutions leading in fields like biochemistry, enzymology, and molecular genetics. No longer was Germany producing the surfeit of scientists that the pharmaceutical firms could draw upon. Not all the constraints were external. The firms themselves were also slow to change. These transformations are painful for large bureaucratic institutions. They are especially painful for large bureaucratic institutions that have a long record of success.[8]

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[7] Jeffrey L. Sturchio, ed., *Values & Visions: A Merck Century* (Rahway, 1991). Both of the authors have Merck connections. Jeffrey L. Sturchio has recently retired as a vice president for corporate responsibility at Merck & Co., Inc., and Louis Galambos has consulted with Merck on historical projects for many years. Together they have published several articles on the history of innovation at Merck, including "Transnational Investment: The Merck Experience, 1891-1925," in Hans Pohl, ed., *Transnational Investment from the 19th Century to the Present*, in *Zeitschrift für Unternehmensgeschichte*, 81 (Stuttgart, 1994), 227-43. Basil Achilladelis, "Innovation in the Pharmaceutical Industry," in Ralph Landau, Basil Achilladelis, and Alexander Scriabine, *Pharmaceutical Innovation: Revolutionizing Human Health* (Philadelphia, 1999), especially 36-57.

[8] Ibid., 63-89. Alfonso Gambardella, *Science and Innovation: The US Pharmaceutical Industry during the 1980s* (Cambridge, 1995). Rebecca Henderson, "The Evolution of Integrative Capability: Innovation in Cardiovascular Drug Discovery," *Industrial and Corporate Change*, 3, 3 (1994), 607-30. Lynne G. Zucker and Michael R. Darby, "Present at the Biotechnological Revolution," *Research Policy*, 26 (1997), 429-46.

The "American Short Century" in Pharmaceuticals, 1940 to 1990

The United States had begun to build its foundation for innovation in this industry long before World War II. The changes began at the local level with the spread of high schools and the improvements in urban education that came out of the progressive reform movement at the beginning of the twentieth century.[9] Atop this structure was a very large and rapidly expanding system of higher education.[10] Long on size and complexity, but short on quality, American universities and professional schools initially lagged far behind the leading European institutions.[11] Gradually, however, the top American research universities began to catch up with their European rivals. Two of the strengths of the American system were the competition that took place between institutions and its substantial fiscal resources in state budgets and private contributions.[12]

The economic resources for research increased sharply following WWII, when the federal government began to pump money into the National Science Foundation and the National Institutes of Health. During the 1950s, NIH became one of the world's most productive centers for research in the medical sciences.[13] For pharmaceuticals, this expansion of an already formidable science base was of crucial importance. It meant the

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[9] Susan B. Carter, et al., eds., *Historical Statistics of the United States, Earliest Times to the Present* (New York, 2006), vol. 2, 387ff. Claudia Goldin edited this section, and unless otherwise indicated, all of our statistics on the United States are drawn from this remarkable compilation.

[10] Claudia Goldin and Lawrence F. Katz, *The Race Between Education and Technology* (Cambridge, Mass., 2008), 18-30, 163-284.

[11] Prior to 1932, the United States received more Nobel Prizes for peace and literature (8) than it did for science (5). The balance shifted sharply toward science (34 to 10) between 1933 and 1953.

[12] Robert Kohler, *From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline* (Cambridge, 1982), provides an excellent comparative study of the transition. Arnold Thackray, Jeffrey L. Sturchio, P. Thomas Carroll, and Robert Bud, eds. *Chemistry in America, 1876-1976* (Dordrecht, 1985).

[13] Victoria A. Harden, *Inventing the NIH: Federal Biomedical Research Policy, 1887-1937* (Baltimore, 1986), covers the early years. For the transition see

industry would have the scientists it needed to explore the medical ramifications of biochemistry, enzymology, molecular genetics, and virology – four fields in which the United States had taken a lead by the 1960s.[14]

Concerned about the declining yield of fruitful chemical entities from traditional techniques of new drug discovery, leading U.S. pharmaceutical firms began to revamp their research and development operations to take advantage of the most promising sciences. Enzyme inhibition and virology paid off quickest with important breakthrough drugs and vaccines.[15] The blockbuster drugs that came out of cardiovascular research – the statins in particular – had a tremendous influence on the American innovation model. The search was primarily focused on small-molecule compounds that promised very substantial sales. The various competitors crowded into those fields, using extensive detailing organizations and direct-to-consumer advertising to compete for market shares.[16] All of the firms tended to concentrate on a set range of therapeutic agents and none covered all fields. They competed, but not across the board with the entire industry. For a time, research on products such as vaccines dwindled as firms focused more tightly on drugs that would have large sales in the American market, the largest market in the

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[14] On biochemistry and enzymology see Robert Kohler, *From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline* (Cambridge, 1982). See also the same author's *Partners in Science: Foundations and Natural Scientists, 1900-1945* (Chicago, 1991). On virology see A.P. Waterson and Lise Wilkinson, *An Introduction to the History of Virology* (Cambridge, 1978); M.R. Hilleman, "The Science of Vaccines in Present and Future Perspective," *Medical Journal of Australia*, 144 (March 31, 1986), 360-64.

On molecular genetics see Maureen D. McKelvey, *Evolutionary Innovations: The Business of Biotechnology* (Oxford, 1996). Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology* (New York, 1979). Robert Bud, *The Uses of Life: A History of Biotechnology* (Cambridge, 1993).

[15] The work of Sir James Black was crucial to enzyme inhibition, but the British industry did not initially follow up on this significant innovation by broadening the approach. This left an opening for American firms.

[16] See Alfonso Gambardella, *Science and Innovation*.

world without price controls.[17] Every major pharmaceutical manufacturer found it advantageous to have operations in the United States to be close to those markets and to the scientific leaders in medical research.

By the end of the 1980s, the American blockbuster innovation model seemed fated to match the longevity as well as the omnipresence that had been achieved by the German model. This model had produced measurable results – measurable improvements in healthcare in both the developed and the developing world. That was the industry's strongest claim for a continuation of the status quo.[18] The large European pharmaceutical companies that had rumbled into the American market were largely following the dictates of the American approach to innovation. The leading U.S. firms were making inroads on European markets, partly by using nationally oriented subsidiaries, and were making advances in Asia, especially in Japan, as well.[19] So-called designer drugs seemed still to have great potential to deal with major health problems, and existing drugs – especially the statins -- were finding new applications that promised additional revenue for the large pharmaceutical companies that had developed and were distributing them.[20]

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[17] Louis Galambos with Jane Eliot Sewell, *Networks Of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (New York, 1995), 123-51. Given the size of government purchases, the vaccine market had a relatively large element of price control.

[18] Basil Achilladelis and Nicholas Antonakis, "The dynamics of technological innovation: the case of the pharmaceutical industry," *Research Policy*, 30 (2001), 535-588. Robert Balance, Janos Pogany, and Helmut Forstner, *The World's Pharmaceutical Industries: An International Perspective on Innovation, Competition and Policy (Cehltenham, UK, 1992).*

[19] Takuji Hara, *Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development* (Cheltenham, UK, 2003), gives a good picture of some of the problems in Japan in the recent past. See also L.G. Thomas, *The Japanese Pharmaceutical Industry: The New Drug Lag and the Failure of Industrial Policy* (Cheltenham, UK, 2001). On Merck's progress see the following: Jeffrey L. Sturchio, *Values & Visions: A Merck Century* (Rahway, NJ, 1991); and Louis Galambos, "The Authority and Responsibility of the Chief Executive Officer: Shifting Patterns in Large U.S. Enterprises in the Twentieth Century," *Industrial and Corporate Change*, 4 (1995), 187-203.

[20] Eric J. Topol, et al., *Textbook of Cardiovascular Medicine* (2006), 752.

External support for the American model came from the regulatory system in the United States. The Food and Drug Administration had a strong international reputation for its high standards and the quality of its decisions about drug safety and efficacy. Many countries simply used the FDA decisions as the basis for drug approval for their markets. This gave firms – U.S. or foreign – operating out of the United States and working closely with the FDA an advantage in global competition.[21]

There were some problems on the horizon – just a few small black clouds. One of them was provided by the new biotech industry that was developing large molecule drugs and exciting the investment community in the United States.[22] But the development of biotech drugs was lagging the Wall Street hype, and the products that were coming out of biotech had to be administered by healthcare professionals, normally in a hospital or doctor's office.[23] So biotech appeared for some time to pose no competitive threat to the pharmaceutical firms that were still turning out billion-dollar small-molecule therapies that could be taken at home.[24] Insofar as biotechnology promised new approaches to research, pharmaceutical firms could always buy their way into the new branch of their industry. Some had already started.[25]

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[21] L.G. Thomas, "Spare the Rod and Spoil the Industry: Vigorous Competition and Vigorous Regulation Promote Global Competitive Advantage," Working Paper, 1998. Also, by the same author, "Regulation and Firm Size: FDA Impacts on Innovation," *Rand Journal of Economics*, 21 (Winter 1990), 497-517.

[22] Sarah Kaplan, Fiona Murray and Rebecca Henderson, "Discontinuities and senior management: Assessing the role of recognition in pharmaceutical firm response to biotechnology," *Industrial and Corporate Change*, 12 (2003), 203-33.

[23] Paul Nightingale and Surya Mahdi, "The evolution of pharmaceutical innovation," in Mariana Mazzucato and Giovanni Dosi, eds., *Knowledge Accumulation and Industry Evolution*, 73-111.

[24] Henry Grabowski and John Vernon, "Innovation and Structural Change in Pharmaceuticals and Biotechnology," *Industrial and Corporate Change*, 3 (1994), 435-49.

[25] Louis Galambos and Jeffrey L. Sturchio, "Pharmaceutical Firms and the Transition to Biotechnology: A Study in Strategic Innovation," *Business History Review*, 72 (Summer 1998), 250-78. Suma Athreye and Andrew Godley, "Internationalization and technological leapfrogging in the pharmaceutical industry," *Industrial and Corporate Change*, 18 (April 2009), 295-323.

Then too there were two other developments that were impinging and threatening to impinge even further on the large American market for pharmaceuticals. Organized healthcare had been gathering force for several decades, in part because steady increases in the cost of healthcare were militating against a continuation of the traditional system of independent physicians, retail druggists, and physician-controlled hospitals. Organizations like Kaiser Permanente were imposing new controls on this system, as were the Pharmaceutical Benefit Managers (PBMs) which had taken a place between the pharmaceutical suppliers and those patients serviced by large organizations (as were the retirees of General Motors and various state and federal employers).[26] The drive to constrain pharmaceutical costs was in turn propelled by a mounting public and political concern about pharmaceutical prices.[27] The industry had been under fire from AIDS activists through the late 1980s, and various NGOs had picked up on the general issue, joining their voices to those calling for changes in the manner in which new drugs were developed and distributed in the large American market.[28]

A glimpse at one possible future could be seen in what had happened to the vaccine business in the 1970s and 1980s. While vaccines were at that time a small part of the output of the global pharmaceutical industry, they were an important element in preventive medicine and especially in efforts to improve global public health. Since most vaccines were purchased by governments and since most governments kept tight controls on costs, the number of companies researching and producing vaccines had shrunk

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[26] Kevin A. Schulman, L. Elizabeth Rubenstein, Darrell R. Abernethy, Damon M. Seils, and Daniel P. Sulmasy, "The Effect of Pharmaceutical Benefits Managers: Is It Being Evaluated?" *Annals of Internal Medicine*, 124, 10 (May 15, 1996), 906-13.

[27] Nigel Gregson, KeironSparrowhawk, Josephine Mauskopf and John Paul, "Pricing Medicines: Theory and practice, challenges and opportunities," *Nature Reviews Drug Discovery*, 4 (February 2005), 121-30.

[28] Bruce Booth and Rodney Zemmel, "Prospects for productivity," *Nature Reviews Drug Discovery*, 3 (May 2004), 451-56.

drastically.[29] Costs were increasing, liability was a growing problem in the United States, and profit margins were tight and getting tighter. A number of important firms made the perfectly rational decision to invest in new drug development, rather than vaccines.[30] For a time, four producers were providing most of the world's vaccines.[31]

But like the British producers of the early nineteenth century and the German producers of the post-WWII era, the leading firms in the American "short" century largely ignored the warning clouds on the horizon. Confident in their ability to continue churning out new blockbuster drugs through the designer-drug approach (combined with the traditional screening approach), they sailed into the 1990s hopeful that neither their profits nor their pristine reputations for saving and improving lives would be impaired.

Beyond the Blockbuster Era, 1990 to 2009

Both soon were impaired. The end of the short century of the American innovation model came amidst a full-blown public and media crisis for the industry. There was an underlying uneasiness about pharmaceutical prices, and now, paradoxically, the discovery of effective HIV/AIDS treatments generated a new storm of protest. The new therapies were shown to be effective in the developed nations that could afford them. But in the years since WWII, the developed world had taken on new responsibilities for the public health of the developing countries – nations which could neither afford nor administer the life-saving HIV/AIDS drugs. In Africa, where the figures for infection rates and mortality reminded close observers of the European

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[29] Louis Galambos with Jane Eliot Sewell, *Networks of Innovation*, 123-51. See also Paul Offit, "Why Are Pharmaceutical Companies Gradually Abandoning Vaccines?" *Health Affairs*, 24 (2005), 622-30. Recently, this trend has been reversed, as vaccine demand increased and drug innovation leveled off.

[30] Louis Galambos, "What are the prospects for a new golden era in vaccines?" *Eurohealth*, 14, 1 (2008), 12-14.

[31] This form of "concentration by default" was a highly unusual pattern of structural change in business.

encounter with the bubonic plague of the 14th century, there seemed to be no answer to the HIV pandemic.[32]

Slow to respond, the industry's public image sank. Pounded by a broad array of NGOs, newspaper writers, and public officials, the industry had trouble making its case for its innovation model. Soon, public opinion polls indicated that an industry that saved lives, pharmaceuticals, was ranked in the public mind with an industry that took millions of lives each year, tobacco.[33] This had important implications for the industry's political standing.

The industry's problems spilled over onto the FDA, which lost some of its stature in the global market for prescription drugs. Congressional investigations and media concern about the agency's ability to police the industry tarnished the reputation of an organization that no longer seemed to be the gold standard for drug approval. The European Union was meanwhile making long strides in developing a centralized agency for the European market, one of the three largest markets in the world.

The defense of the American model was built around the high rate of innovation. In effect, the advocates for the status quo said, the American market was subsidizing innovation for those countries that squeezed margins so hard that firms could not afford extensive R&D operations. That claim initially had some appeal, but then the rate of innovation started to drop off, leaving the industry in an even more perilous position. Throughout its modern history, the science base of the industry had evolved in a series of

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[32] John Iliffe, *The African AIDS Epidemic: A History* (Athens, Ohio, 2006). Helen Epstein, *The Invisible Cure: Africa, the West, and the Fight Against AIDS (New York, 2007).*

[33] As journalist Gardiner Harris observed (*New York Times*, "Drug Companies Seek to Mend Their Image," July 8, 2004): "no industry has fallen as far or as fast in public esteem in recent years as the pharmaceutical industry…." See also Roger Pilon, "Drug Reimportation: The Free Market Solution," *Policy Analysis*, 521, August 4, 2004.

long cycles, punctuated by flat periods in new drug development. That is what had happened in the 1970s, before the industry made a successful transition to biochemisty/enzymology as its guiding science. Now the biochemistry/enzymology cycle was hitting a similar flat phase. With fewer blockbusters and the impeding threat of patent expirations hanging over all of the major producers, the rationale for the American innovation model lost much of its appeal. This situation undercut the justification for the armies of detail men and women the major companies had unleashed on healthcare professionals in the developed-nation markets.

The Search for a New Innovation Model

The cracks that had appeared in the American model set in motion the search process that now characterizes the industry. Some companies are sticking with the classic blockbuster model – with heavy investment in in-house R&D, bringing a few blockbusters to market, then selling them with great intensity around the world. In this case, however, the sales are still primarily anchored in the U.S. marketplace.

The modified European version of this is similarly based on large blockbusters and increasingly large combinations of other corporations (GSK, Sanofi Aventis, Novartis).[34] There is, however, a twist in that they tend to have a more diversified portfolio. For example, Roche has invested heavily in Genentech, Novartis in Sandoz (and buying Hexal), and GSK has moved into consumer products.[35]

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[34] Simon Frantz, "Pipeline problems are increasing the urge to merge," *Nature Reviews Drug Discovery*, 5 (December 2006), 977-79.

[35] For an excellent general analysis of concentration in pharmaceuticals see Franco Malerba and Luigi Orsenigo, "Innovation and Market Structure in the Dynamics of the Pharmaceutical Industry: Towards a History Friendly Model," *Industrial and Corporate Change*, 11 (2002), 667-703.

As returns in European markets and Japan began to soften, there was a continuation of the attempt to buy a presence in the U.S. marketplace. Most of the Japanese firms did this, and the Europeans as well – that was, after all, a major part of the rationale for Glaxo and Wellcome to combine, as well as SKF and Beecham.

But now the global market was becoming much more complex. Using the opposition-psychology generated by the early phase of the HIV/AIDS crisis, firms in the developing world had begun to push generics into the markets heretofore controlled by the major Western multinationals.[36] The argument for abandoning World Trade Organization standards for the protection of intellectual property was that this was a matter of life or death for the citizens of the developing world. But as it turned out, that was just a transitional argument for a transitional development.[37]

As they moved ahead, the Indian, Chinese and Israeli entrepreneurs began to realize that they would never reach the scale to which they aspired as long as they played only in generics and only in their home markets.[38] Hence, the global expansion and consolidation of the generic business. This was followed by another phase as certain generic producers (e.g., Ranbaxy) began to realize that the returns they were looking for required investment in new products as well as global scale.

The biotech industry, through all of this, seemed to be banking on a business model that was evolving in the direction of traditional big pharma – see, for example, the

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[36] Suma Athreye, Dinar Kale, and Shyama V. Ramani, "Experimentation with strategy and the evolution of dynamic capability in the Indian pharmaceutical sector," *Industrial and Corporate Change*, 18 (2009), 729-59. Sarah E. Frew, Hannah E. Kettler, and Peter A. Singer, "The Indian and Chinese Health Biotechnology Industries: Potential Champions of Global Health?" *Health Affairs*, 27 (2008), 1029-41.

[37] See http://iipi.org/activities/forums/IP&Public_health/papers/galambos.pdf. See also *Wall Street Journal*, June 24, 2005, A13; October 12, 2005, B3.

[38] On these developments see the papers delivered by Shereen El Feki ("Prescription for Change") and Ian Ragan ("Innovative Medicines for Europe") at the Institute of Medicine's Forum on Drug Discovery, Development, and Translation, June 30, 2005, at www.iom.edu/drug.

strategies of Amgen and Biogen Idec. But overall, the direction seems to have been evolution into a symbiotic relationship with big pharma based on a division of labor. Biotechs, which take on a great deal of the risk of new drug development, have the flexibility and agility to pioneer completely new therapeutic approaches. Their big pharma partners have the global scale and scope to bring these to market successfully. That set of relationships seems to have become more stable in the past few years.[39] This is the nature, for instance, of Merck's licensing and alliances work in the past decade. The company is trying to create a steady supply of new technologies and products more efficiently than through the traditional approach of depending almost entirely on internal R&D capabilities.[40]

Some preliminary conclusions

The patterns of innovation and market dominance we've seen in the history of the global pharmaceutical industry are the contingent outcome of a series of interactions among key networks in science, in public policy and in commercial relations. Firms that have prospered over time are those that have been most adept at engaging with and adapting to these networks of influence and to the organizational clusters that accompany them. The German and Swiss firms that pioneered the late nineteenth century and early twentieth century approach to science-based innovation drew on the organic chemistry research

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[39] Andrew Jack and Christopher Bowe, "Shock treatment: drugs companies seek new remedies to restore growth," *Financial Times*, April 21, 2005, 13.

[40] See "New models for early-stage collaborations at Merck: flexibility and creativity," *Nature Reviews Drug Discovery*, 10/08, http://www.merck.com/licensing/pdf/new_models.pdf. See also Luigi Orsenigo, Fabio Pammolli, Massimo Riccaboni, Andrea Bonaccorsi and Giuseppe Turchetti, "The Evolution of Knowledge and the Dynamics of an Industry Network," *Journal of Management and Governance*, 1 (1998), 147-75.

conducted at local universities, the process-expertise developed in world-class chemical manufacturing in their regions, and government policies that favored export businesses. Fifty to sixty years later, the rise to leadership by US-based pharmaceutical firms benefited from the massive investment in clinical and scientific research led by the U.S. Congress, the presidents, and the postwar NIH. State and local governments contributed to the development of a massive system dedicated to higher education, professional training, and research.[41] Together, these leaders and institutions created a political climate that favored high-tech industry and fostered a robust economic, commercial and policy environment that enabled rapid and impressive expansion in the industry's global presence.

The next phase of the pharmaceutical industry's evolution will doubtless be shaped by a similar set of networks and clusters - but with a special, new twist: the outcomes will now be determined on a more fully globalized stage.[42] The demand is now shifting to emerging markets and developing countries, as traditional markets in North America, Europe and Japan mature and as the so-called "pharmerging markets" and other new markets expand and broaden their investments in health.[43] A recent article from *The Economist* predicts that only 9% of the sales growth in the industry in 2009 will come from the United States, only 14% from the EU (5), and only 9% from Japan. Emerging countries (China, Brazil, India, South Korea, Mexico, Turkey, and Russia) will

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[41] The best overview of the entire system is provided by Claudia Goldin and Lawrence F. Katz, *The Race between Education and Technology*.

[42] See, for instance, Monali Ray, Abdallah S. Daar, Peter S. Singer, and Halla Thorsteinsdotttir, "Globetrotting firms: Canada's health biotechnology collaborations with developing countries," *Nature Biotechnology*, 27, 9 (September 2009), 806-14.

[43] My most recent message from PharmAsia News say that "The Pharma Market in Asia will be $929 Billion by 2012." Even after making a Standard Hype Discount, the figure is very suggestive.

provide 34% of the growth.[44] The free market in drugs and vaccines that has long been a characteristic of the US market is likely to look more like the regulated markets of Western Europe and other developed economies in the next few years, as a result of health care reform spearheaded by the Obama Administration. That will simply add to the momentum for a global readjustment of sources of growth in pharmaceuticals and vaccines.

On the science front, we are already seeing the impact of the global redistribution of resources. Entrepreneurs and university leaders in India, China, Brazil, the Asian Tigers and Africa are beginning to build the organizational infrastructures that will enable them to compete with the traditional powers in clinical and scientific research for pharmaceutical and vaccine innovation.[45] The newcomers are aided by the global reach of the Internet and the related transportation and communications revolutions that make it possible for researchers in Boston, Beijing and Bangalore to be part of the same cutting-edge innovation networks. Given this increased intellectual competition, traditional leaders in pharma and vaccine R&D will seek more partnerships: with biotech firms, with new technology platforms; with healthcare providers and with others who can help them bring new niche innovations to market efficiently and profitably. More and more of these partnerships will be with universities, especially in the United States.

Because of demographic trends – an aging population beset by chronic conditions

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[44] *The Economist*, "Racing down the pyramid," *The Economist*, November 13, 2008, http://www.economist.com/business/displaystory.cfm?story_id=12601852. An updated forecast from IMS Health (after the global financial crisis had hit) puts the growth contribution from the "pharmerging markets" at half of the industry's growth in 2009, with the expectation that the average contribution to growth from these markets will be 40% through 2013. See "IMS Health lowers 2009 global pharmaceutical market forecast to 2.5 – 3.5% growth," Press release, April 22, 2009, http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=1e61fa8adbec0210VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1 .

[45] Fabio A. Thiers, Anthony J. Sinskey and Ernst R. Berndt, "Trends in the globalization of clinical trials," *Nature Reviews Drug Discovery*, 7 (January 2008), 13-14.

like asthma, diabetes, and cardiovascular disease – and the financial pressures of a global economic crisis, the ground rules for industrial, economic and health policy will favor the trend toward expanding coverage for proven medical interventions. This will continue to be accompanied by efforts to find ways to control the seemingly runaway costs of health care. While innovation will still be welcome, it will need to have a sounder evidence base to persuade policymakers and payers to adopt it for most populations.[46] The bias toward new technologies that has characterized a century of pharmaceutical history will continue to shift toward an emphasis on value for money in an environment more focused on allocation of increasingly scarce resources (per capita).

Those firms that can anticipate and adapt to these trends in the coming years will continue to do well. Just as the ecology of innovation changed dramatically at earlier inflection points in the eventful history of pharmaceutical entrepreneurship, we can expect similar dramatic changes in the future of this important industry.[47] This is the only thing we can predict with certainty.

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[46] See, for example, Michael Dickson and Jean Paul Gagnon, "Key factors in the rising cost of new drug discovery and development," *Nature Reviews Drug Discovery*, 3 (May 2004), 417-29. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 22 (2003), 151-85.

[47] The expression "inflection points" comes from Andy Grove of Intel. See his insightful account in *Only the Paranoid Survive: How to Exploit the Crisis Points that Challenge Every Company* (New York, 1999 edition).