

POLICY

How to handle an industry in disruption: Intervene or laissez-faire?

Bernard Munos^{1,2}

An analysis of four regions in four countries suggests that the best way to mitigate disruption of the pharmaceutical industry is not to ignore or stem it but to sponsor initiatives that keep scientists engaged.

The building of biomedical innovation clusters has been a goal of many government planners. The regions that have succeeded in these efforts have enjoyed economic growth and high-paying jobs while attracting follow-on investments in technology. However, as the pharmaceutical industry—which powers many of these clusters—undergoes a profound transformation, the rules for nurturing clusters are changing. In some areas, such as Sweden, England, and Quebec, industry consolidation has led large pharmaceutical companies to shutter once-productive research and development (R&D) sites and move them elsewhere. This shuffling has left deep holes in the economic fabric, putting the viability of what remains in jeopardy. Yet out of this misfortune, new research models have risen that are patching the holes and reinvigorating innovation. This Perspective describes how creative policy-making can facilitate such recovery.

CHALLENGING TIME FOR INDUSTRY

In the past 15 years, the pharmaceutical industry has transformed from an admired, thriving industry to one facing stagnant revenues along with price and intellectual property (IP) challenges. Many factors have combined to produce this reversal of fortune.

Internal challenges. R&D productivity has been on a long-term decline (1). The industry's struggle to improve its new drug output (Fig. 1) has led many companies to consolidate work sites and abandon therapeutic areas. For instance, Pfizer closed multiple facilities, including ones in Ann Arbor, Michigan (United States), Sandwich (UK), and Singapore; AstraZeneca shuttered laboratories in Montreal (Canada), Lund (Sweden), and Bangalore (India); Roche shut down a facility in Nutley, New Jersey (United States), and Novartis ended operations in Horsham (UK).

¹FasterCures, Milken Institute, Washington, DC 20005, USA. ²InnoThink Center for Research in Biomedical Innovation, Indianapolis, IN 46228, USA.
E-mail: bhmunos@stanfordalumni.org

Spread of collaborative research. The digitization of biology and medicine has created vast opportunities to better understand diseases and design new therapies. However, much of this work has been spearheaded by academia and small companies and has resulted in increasingly complex collaboration networks among the many players engaged in biomedical research. Big Pharma has responded by externalizing a growing share of its drug discovery efforts and refocusing internal R&D on clinical development—a change sometimes described as a “shift from bench to bedside” (2). This has changed innovation dynamics and moved the locus of innovation from in-house R&D to the networks because these expanding collaborations increasingly are led intellectually by external collaborators rather than by the big pharmaceutical companies themselves (3).

Economic challenges. Patent cliffs and tougher reimbursement policies have caused a steep increase in the share of prescriptions filled by generic drugs. In the United States, that percentage has grown from 47% in 2001 to 83% in 2013 (4). To mitigate the negative impact on their revenues, pharmaceutical companies have raised prices aggressively, causing a widening gap between generic and brand prices. Since 2008, for instance, generic-drug prices in the United States have halved, whereas brand prices have doubled (5). This gap has accelerated the shift to generics, making a difficult situation worse.

Policy challenges. The high prices of many branded drugs have triggered a backlash in a growing number of countries. In some, governments have rescinded patents or used compulsory licenses to make drugs affordable for their citizens; in others, they have used their authority as payers to curtail reimbursements. Whereas these challenges were initially limited to emerging economies, they are now spreading to developed markets such as Western Europe, Canada, and Australia.

THE NEW RUST BELTS?

These challenges have precipitated major changes in the pharmaceutical industry. The giant research sites that were common across leading companies—where scientists

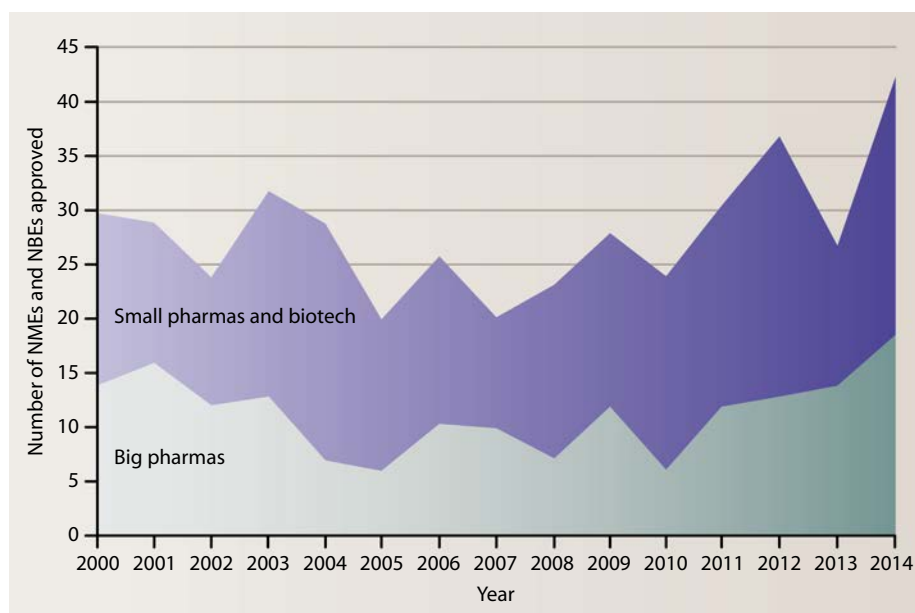


Fig. 1. By the numbers. New molecular entities (NMEs) and new therapeutic biologic entities (NBEs) approved by the U.S. Food and Drug Administration (Source: FDA). Big pharmas: AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers, GSK, Johnson & Johnson, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi.

once enjoyed serene, campus-like environments—became cathedrals built for another age. Their internally focused designs were ill-suited to the increasingly collaborative nature of biomedical research. These often-conservative centers were organized around rigid processes and suffused by a lavish culture that fostered profligate habits and lessened the incentive to change (6).

In many cases, the new R&D leaders who were tasked with reversing the decline in productivity concluded that retooling that old infrastructure was not an option. Policy-makers and civic leaders were dismayed by the closures that followed, but their reactions in different parts of the world offer illuminating insights into how policy-making can turn dire situations into new opportunities.

England. For the past century, England has been a powerhouse of the pharmaceutical industry. Building on the Nobel prize-winning science of its universities, companies such as Imperial Chemical Industries, Burroughs-Wellcome, Glaxo, and Beecham invested massively in research. They were joined by foreign companies eager to leverage England's talented workforce. The result was the buildup of an impressive research infrastructure that included some of the largest facilities in Europe. These campuses were scattered around the country, often in isolated pastoral settings. For decades, this isolation did not matter because much of the research was performed in-house. However, as size and scale became less effective at fostering innovation, that infrastructure became a drag.

The industry no longer needed giant facilities, but smaller ones, located near research universities and surrounded by a rich fabric of small companies and academic medical centers. Bold science and interaction among those involved in it had replaced economies of scale as the drivers of innovation. The old infrastructure—likened by GlaxoSmithKline (GSK) chief executive Andrew Witty to “a big pile of bricks with air conditioning” (7)—had become largely useless. Pfizer closed most of its 2400-employee laboratories in Sandwich, Kent, as well as a similar facility in Groton, Connecticut, and opened a new research center in Cambridge, Massachusetts. Likewise, AstraZeneca closed its 2900-employee R&D site in Alderley Park, Cheshire, and built a new one in Cambridge, UK. The British government and The Wellcome Trust added their own touch by locating the new \$1 billion Francis Crick Institute in Central London. When completed, it will be the third

vertex of a “scientific ‘golden triangle’ whose other corners are Oxford and Cambridge” (7). It will provide jobs to 1250 scientists—a welcome opportunity for some but only a fraction of the jobs lost in the closures.

New Jersey. The New York City–Philadelphia corridor is the historic home of much of the U.S. pharmaceutical industry. So when trouble developed, it hit the area with full force, leaving thousands of highly educated people without the comfortable incomes and job security that had been a hallmark of the industry. Unmoored, they drifted toward career coaches and support groups, sharing experiences and tips to get interviews, just as new waves of layoffs emptied more laboratories and plants.

Between 2007 and 2012, New Jersey and Pennsylvania shed 22,000 pharmaceutical jobs, mostly from large companies. Yet during the same time, 300 life science companies sprouted across the region. Many were contract research organizations that did work that drug companies used to do internally but are now keen to outsource to lower-cost organizations. Other companies were founded by frustrated researchers who saw a chance to pursue scientific ideas that their former employers would not consider. Many unemployed scientists found new jobs in those start-ups, but often at lower salaries than those they used to enjoy. Some left the area for other states where they could secure employment in their areas of expertise. Yet, others exited the industry permanently, tak-

ing teaching positions, early retirement packages, and, sometimes, menial jobs that they needed in order to pay the bills.

Montreal. With its French roots, English-speaking universities, and international business community, Montreal's cosmopolitan society is the kind of environment where innovation flourishes. Indeed, over the past century the Canadian province developed a rich cluster of leading academic and biomedical institutions along with pioneering homegrown companies. This unique terroir attracted outside interest, and in 1965, Merck swooped in and bought Charles E. Frosst, a leading local company. Merck-Frosst went on to become a world-class R&D laboratory and the birthplace of some of its parent's best-selling drugs, including Singulair and Timoptic. Other companies followed, and by the start of the new millennium, AstraZeneca, Bristol-Myers Squibb, GSK, Johnson & Johnson, Novartis, Sanofi, Shire, and Wyeth had joined more than a hundred biotechnology companies and public institutions (8) to create “a life science haven” (9). When the innovation crisis hit, however, Montreal was not spared. Large pharmaceutical companies facing patent cliffs found it hard to justify keeping R&D facilities in Montreal and nearby Boston. Many chose to consolidate on the U.S. side of the border. Merck and AstraZeneca closed their operations, and others scaled down, causing a 28% drop in the number of pharmaceutical, medical, and manufacturing jobs in Québec between 2006 and 2011 (9).



A winning strategy: Geneva makes the right move.



Fast forward: Montreal speeds into the future.

The area's leaders were prompt to react. Recognizing that research was undergoing a radical transformation, they created institutions to keep local scientists engaged and in the vanguard of innovation. Two unusual organizations emerged: CQDM, which is focused on precompetitive research, and NEOMED, which is centered on early translation (table S1). Both have reconfigured drug R&D by enabling networks that promote collaboration and cross-pollination among academics, biotech entrepreneurs, big Pharma, and other stakeholders. And, it seems to be working. Barely 5 years after the contraction of its biomedical sector, Montreal is on the rebound. Almost half of Canada's life sciences industries are concentrated there, as well as the majority of the basic and clinical research activities conducted in the country. Altogether, Montreal is now home to more than 400 companies developing over 150 products and technologies (9).

Geneva. In 2012, Merck KGaA announced that it would close the headquarters and research center of its pharmaceutical division, Merck-Serono, in Geneva, Switzerland. Nearly 1250 employees would lose their jobs. Their first reaction was to fight and strike. But the reality quickly sunk in, and the community organized. A couple of local billionaires stepped in and joined hands with universities to acquire the facilities and create Campus Biotech SA, an ambitious public-private research center that has become the heart of the Swiss “neuro-

science valley.” Half of it houses academic neuroscience research programs as well as the Wyss Institute for Bio- and Neuroengineering—which was created by a \$103 million donation from Hansjörg Wyss, a medical devices entrepreneur who also funded the Wyss Institute for Biologically Inspired Engineering at Harvard University. Ernesto Bartarelli—a businessman, philanthropist, and majority owner of Serono when Merck KGaA bought it in 2007—is pitching in with several tenured positions.

The rest of the facility will house startups, established companies, and clinical research facilities. The idea is to create an interactive innovation ecosystem in which scientists enrich each other and spark ideas that fuel innovation. Six startups have been created from assets divested by Merck-Serono (10). They are backed by a €30 million venture fund created by the company for that purpose. Campus Biotech SA is also attracting interest from other investors. Sofinnova and Novo have recently teamed up to invest \$34.5 million in ObsEva, a biotech company founded on Merck's former preterm labor drug research. It is too early to fully assess the success of the program, but it looks encouraging. Campus Biotech hosts more than 400 employees, a figure that is expected to rise quickly to 600. Cutting-edge research continues to be done at the facility and in several nearby biotech communities, talent remains engaged, entrepreneurs are getting a chance to create, and funding is available to support them.

POLICY IMPLICATIONS

Over the past 15 years, the pharmaceutical industry has undergone a sweeping reconfiguration driven by changes in science, new research models, and escalating economic pressure. Seven large pharmaceutical companies have disappeared, a number that may still rise. The R&D model, which used to rely on large facilities staffed by thousands of scientists, is being replaced rapidly by interconnected networks of partners anchored around major universities and medical facilities. This redistribution of activities has not been painless. Areas such as England, where much of the research was performed away from academic medical centers, have had to write off a lot of the old infrastructure and rebuild it anew closer to the countries' leading universities. The displacement and job losses have been severe—and the loss of talent even worse.

In retrospect, there was little that could have been done to prevent this. When the infrastructure was laid down many decades ago, there was no way to predict the present. Disruptions spawned by changes in business models happen. The best that policy-makers can do is to avoid making them worse. In this case, that means refraining from using public funds to keep old facilities afloat and, instead, using financial resources to ease the relocation of talent to the new centers. This is not what happened in England as policy-makers and community leaders tried to soften the blow by creating new research jobs in the old laboratories. Recent reports suggest that these efforts have been largely ineffective (11).

The situation in New Jersey is hardly better. American policy-makers' aversion to interfering with free markets left many jobless scientists fending for themselves while their jobs migrated to new campuses, such as New York's Alexandria Center (12). Those who created contract research organizations (CROs) hoped to lure business from their former employers. This plan worked to some extent, but CROs are about cost-cutting, not innovation. Although some jobs were preserved, many of those tied to innovation moved away, dimming the state's prospects. It did not need to be so. New Jersey's pharmaceutical sector is dense enough, and the state has enough fine universities, that it could have attempted what New York and England have done. Doing so might have been costly, but likely less so than the present value of the jobs that migrated.

Montreal fared much better. In a way, it was fortunate that the lost jobs were located close to its universities and medical facilities. But it also took vision and leadership to recognize that research was changing and to create institutions that facilitated biomedical research's transition toward the new, networked model. The result is a biomedical cluster that is well positioned relative to its competition, and its recent performance seems to validate the choices that were made. Another remarkable factor in the Montreal experience has been the lack of acrimony as the various stakeholders worked together to pull through a difficult situation. Even the companies that moved away kept a stake in the area by financially supporting and advising CQDM and NEOMED. These companies are now benefiting in a win-win scenario that is attracting follow-on investors. Versant Ventures recently brought to Montreal Inception Sciences "its booming startup factory" because of "the strong capabilities that exist" there (13).

Like Montreal, the Geneva area has benefited from its urban setting and academic and medical institutions. Having benefactors who saw an opportunity in adversity and stepped in to help did not hurt either. The experiment is still unfolding, but the results already achieved are encouraging. Merck KGaA's decision to create a venture fund in order to help with the transition was another important step in rallying community support. Ultimately, as in Montreal, it was a combination of public and private funding as well as initiative that allowed the community to adjust, while keeping scientists engaged.

THE LESSONS

Business disruptions happen and should be allowed to run their course. They are an es-

ential part of the creative destruction that rejuvenates industries and makes for a vibrant economy. Policy responses are often guided by a laissez-faire attitude or by initiatives undertaken on behalf of the incumbents in order to preserve the status quo. This analysis of the ongoing disruption of the pharmaceutical industry suggests that a response that cuts across the ideological divide leads to better outcomes. Part of the reason is that collaboration among stakeholders helps preserve the fabric of the community and keeps scientists creating. Networks are an essential part of the innovation process (3) and, once disrupted, can take a long time to rebuild. During that time, little happens: Innovation slacks, the cluster loses its sheen, young scientists are tempted to go elsewhere, and investors find fewer opportunities to engage their capital. If the situation is well managed, however, that transition can be a potent source of competitive advantage. Montreal's quick rebound is a case in point. Not only has it kept its scientists busy, it has made it easier to translate their breakthrough ideas into commercial products, thanks to the networks, capital, and facilities offered by CQDM and NEOMED. Although other geographical areas continue to struggle to adjust, Montreal—and Geneva—are powering ahead.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/7/286/286ps12/DC1

Table S1. Public-private partnerships CQDM and NEOMED

REFERENCES

1. J. W. Scannell, A. Blanckley, H. Boldon, B. Warrington, Di-

agnosing the decline in pharmaceutical R&D efficiency. *Nat. Rev. Drug Discov.* **11**, 191–200 (2012).

2. I. Rafols, M. M. Hopkins, J. Hoekman, J. Siepel, A. O'Hare, A. Perianes-Rodríguez, P. Nightingale, Big pharma, little science? A bibliometric perspective on big pharma's R&D decline. *Technol. Forecast. Soc.* **81**, 22–38 (2014).
3. W. W. Powell, K. W. Koput, L. Smith-Doerr, Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology. *Adm. Sci. Q.* **41**, 116–145 (1996).
4. Generic Pharmaceutical Association, 2013 Annual Report; available at www.gphaonline.org.
5. The Express Scripts Prescription Price Index, 2013 Drug Trend Report (8 April 2014); available at <http://lab.express-scripts.com/drug-trend-report/trend-drivers/the-express-scripts-prescription-price-index>.
6. P. Hollinger, Pfizer strategy revives fears for future of life sciences in UK. *Financial Times* (25 May 2014).
7. A. Jack, A. Drugs, Supply running low. *Financial Times* (9 February 2011).
8. J. Niosi, T. G. Bas, Biotechnology megacentres: Montreal and Toronto regional systems of innovation. *Eur. Plann. Stud.* **11**, 789–804 (2003).
9. H. Carmichael, Pharma firms see mixed fortunes in Québec. *Chemistry World* (8 May 2012).
10. Six startups in Geneva, Switzerland created from Merck assets: Prexton Therapeutics, Quartz Biol., Asceneuron, TQM Insight, Ondaco, and Calypso Biotech.
11. N. P. Taylor, Role of ex-big pharma sites questioned as property companies snap up science parks. *FierceBiotech* (10 July 2014); available at www.fiercebiotech.com/story/uk-pols-ready-pfizers-return-az-cozies-eu-academia-israeli-biotech-upsizes/2014-07-10#3.
12. G. Delaporte, Welcome to the Biol-Dome. *Commercial Observer* (22 October 2013); available at <http://commercialobserver.com/2013/10/welcome-to-the-bio-dome>.
13. J. Carroll, Versant's inception plants its booming biotech startup model in Montreal. *FierceBiotech* (25 June 2014); available at www.fiercebiotech.com/story/versant-s-inception-plants-its-booming-biotech-startup-model-montreal/2014-06-25?utm_medium=nl&utm_source=internal.

10.1126/scitranslmed.aaa3679

Citation: B. Munos, How to handle an industry in disruption: Intervene or laissez-faire? *Sci. Transl. Med.* **7**, 286ps12 (2015).