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Where is the Pharmacy to the World? International Regulatory Variation and Pharmaceutical Industry Location

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Abstract

A consumer-oriented model for drug development and use has attracted attention in recent years as an alternative to the much-maligned approach of mass-marketing blockbuster drugs. In a parallel development, patients and disease-based organizations have assumed greater roles in defining disease categories than in the past and now influence clinical trials and participate in regulatory decision-making. Yet these developments are far from universal and are taking very different forms around the world. Building on data showing that pharmaceutical firms headquartered in the United States have performed well since 1980 when compared to firms in Europe or Asia (measured both by sales and by numbers of new product introductions), this essay explores the interplay of regulation, definitions of "patient" and "consumer," and centers of power for the pharmaceutical industry. A comparison of the United States and Germany in particular, and the United States and European Union more generally, suggests that how countries resolve tensions between protecting patients and empowering consumers will impact the international competitive standing of their domestic pharmaceutical industries.

I. Introduction

Pharmaceutical companies have long operated simultaneously as free-market sellers of therapeutic molecules and as tightly regulated providers of a critical healthcare component. Their success at inventing and marketing medicines over the past century has made them highly valued contributors to national economies. In recent years, however, rising drug costs, market withdrawals due to adverse reactions, and concerns that industry research is focusing on lifestyle treatments at the expense of curing life-threatening diseases have combined to put pharmaceutical firms under increased scrutiny worldwide. Critics argue that the industry has tilted too far toward the free-market side of its operating mandate. Proposed solutions in the United States, Europe, and elsewhere include drug price controls, more rigorous enforcement of existing safety laws, and new regulations for post-market monitoring. While there are overarching similarities around the world in concerns with drug safety and availability, differences in regulatory systems and drug markets continue to significantly impact firm strategy and the relative performance of pharmaceutical or biotechnology companies from different countries.

This essay explores the relationship between national pharmaceutical sector performance and the current era of "consumer" regulatory approaches through a comparison of the United States and Germany. Specifically, it focuses on a counterintuitive development since the early 1980s as Germany, historically the "pharmacy to the world," witnessed a decline in its domestic pharmaceutical industry. Particularly when compared to its historical performance or to other European countries such as Switzerland and the United Kingdom, the German pharmaceutical

sector brought fewer new drugs to market in the past three decades than previously. The pharmaceutical industry in the United States, by contrast, generated gains relative to Germany and other European countries and relative to its historical performance. Whereas close to one-third of new drugs were invented by pharmaceutical firms headquartered in Germany in the 1960s and 1970s, this figure dropped to thirteen percent in the 1990s and has declined further since that time.

The United States and Germany offer excellent dimensions of similarity and difference that shed light on the relationship of innovation to regulation. Both have sophisticated medical systems characterized by advanced technologies, significant spending on biomedicine, and support for new therapies in the form of government funding for research and large patient markets covered by third-party insurance. They consistently rank as the largest pharmaceutical markets in the world.[1] Pharmaceutical firms in both countries are global producers and marketers of drugs as well as employers to thousands of scientists. Yet, these two countries also differ in important ways. The role of the government as regulator has varied significantly, with the U.S. Food and Drug Administration (FDA) centralizing safety regulatory authority while Germany relied on a more networked approach among physicians, industry, and government officials to determine drug safety and efficacy. The involvement of patients as political actors in debates over innovation and regulation has also differed, with disease-based organizations playing a growing role in the United States, but a comparatively minor role in Germany.[2]

From its historical origins in Germany and Switzerland, the modern pharmaceutical industry has evolved into a global business.[3] Even though pharmaceutical firms often locate research labs, clinical development, and manufacturing in a variety of countries, many of the benefits – employment of skilled labor employment, development of new technology and cutting edge medicine, tax revenues, and overall economic growth – accrue to the home country where firms are headquartered.[4] Nations thus compete for pharmaceutical industry research laboratories and manufacturing sites in order to benefit from the economic growth they stimulate, the scientists and other skilled workers they employ, and to ensure access to the medicines they invent and manufacture. In some cases, governments have sought to protect the firms located within their borders when cross-national mergers were proposed, viewing them as national assets.

While very similar formal requirements for drug quality, safety, and efficacy were in place across nearly all industrialized countries by 1980, countries continue to regulate pharmaceutical research, clinical testing, marketing, and pricing through quite different mechanisms.[5] Government regulation of this sector remains largely national and other forms of oversight, including by the medical profession, pharmacists, and organizations directly representing patients, are likewise based on national or even regional institutions. Despite an ongoing international harmonization process for pharmaceuticals, the past decade has seen the continuation and even expansion of these national regulatory systems.[6] As a result, cross-national comparative analysis of regulation reveals important insights on how national polities define “the patient” who benefits from safe, effective, and affordable therapies and “the consumer” who should be protected from harm but otherwise have a variety of available therapeutic choices.

The comparisons developed in this essay of the United States and Germany specifically, and the United States and Europe more generally, illuminate tensions associated with consumer-driven regulation that are shaping the competitive landscape for pharmaceutical companies. It is striking that just as patient and disease-based activists have taken on certain regulatory functions traditionally associated with the state or peak medical associations, a greater consumer and market orientation in medical care has increasingly put the onus on patients to independently seek out information about pharmaceuticals and to treat prescription drugs like other goods they purchase. However, little scholarship to date has connected these developments with the industry's economic performance or business strategy. Though in part speculative at this point, the data and analysis presented here are an initial step toward deepening the understanding of interrelationships among government regulation, patients' mobilization both as regulators and consumers, and the functioning of the pharmaceutical industry.

This essay has two further ambitions. First, I present summary data and brief analysis of the pharmaceutical sector in its national contexts. Some critics of the industry have argued that by chasing global markets and by moving research and manufacturing facilities to countries with lower labor costs, firms were able to shop for weaker national regulatory systems and exert deregulatory pressure. Instead, it appears that the pharmaceutical industry has remained largely concentrated in the United States and Europe, which historically set high barriers to drug approvals. Second, the essay seeks to connect academic literature in the history and economics of innovation with studies of regulation. Both areas have seen interesting work in recent years, but little has been done to integrate perspectives from the two areas.[7] As a result, studies of regulatory systems often fail to assess the impact of changes on industry structure and strategy; likewise, studies of innovation rarely explore international variation in regulation and the interplay of regulation with product development.

To examine the interplay of industry, regulators, and the consumer/patient, the next section provides and analyzes key indicators of national and international pharmaceutical industry performance, with a focus to the national headquarters of firms. These data present a puzzle regarding why firms headquartered in the United States had notably better results since the early 1980s than their competitors in Germany and to a lesser extent, other European countries. The third section contrasts how the United States and Germany addressed three interrelated, but discrete issues: the emergence of a new disease (HIV/AIDS), demands by patients with terminal diseases for access to treatments still undergoing testing, and emerging concepts of personalized medicine. In each of these three areas, regulatory innovations were made in the United States fostering a "consumer" mode within an overall framework of predictable, procedure-based decision processes. A regulatory approach defined around protecting "patients" in Europe, and the complexities of shared authority among the medical profession, other peak associations, and the state in Germany may have unwittingly contributed to a weaker domestic pharmaceutical industry. The conclusion argues that understanding the relationship of innovation to regulation in different countries is critical to moving beyond current crises in regulatory policy to the benefit of patients for whom medicines are intended.

II. Locating Pharmaceutical Production and Consumption

In the late 1970s and early 1980s, a series of studies by the U.S. government, think tanks, and academic economists warned that the United States was losing its competitive edge in the pharmaceutical sector. Measured in some cases by the number of leading companies (in sales and new product introductions) headquartered in the United States, and in others by a lag between European drug approvals and FDA decisions, this research suggested that a mix of excessive regulatory precaution, rising expenses of clinical testing, and a generally weak innovation climate were eviscerating the industry.[8] A number of analysts warned that firms would move research and development, product testing, and manufacturing out of the country with significant negative impacts. Yet some thirty years later, a set of similar measures presented here suggests that the U.S. pharmaceutical sector instead prospered in the period since 1980, a trend that appears to have accelerated since the early 1990s.

Performance of pharmaceutical firms and the industry as a sector can be measured in a number of ways, with sales and new product introductions offering two particularly salient metrics. Additional measures, including the size of the national pharmaceutical market and the attractiveness of a country for clinical research, help to deepen this analysis and connect to the discussion of regulatory approaches in the face of a new disease, societal pressures for compassionate use programs, and the use of biomarkers as a component of personalized medicine that follows in the next section.

Table 1. Top 15 Pharmaceutical Firms by Sales, 1974[9]

Rank	Company Name	Location	Pharmaceutical Sales ($ millions)
1	Roche	Switzerland	1,386
2	Merck	U.S.	1,197
3	Hoechst	Germany	1,174
4	Ciba-Geigy	Switzerland	1,063
5	Bayer	Germany	862
6	Sandoz	Switzerland	847
7	Eli Lilly	U.S.	789
8	American Home Products	U.S.	758
9	Pfizer	U.S.	740
10	Upjohn	U.S.	683
11	Warner Lambert	U.S.	611
12	Rhone-Poulenc	France	595
13	Sterling	U.S.	566
14	Abbott	U.S.	551
15	Boehringer-Ingelheim	Germany	506

In a striking development considering the industry's origins in Germany, France, and Switzerland, the past fifteen years have witnessed a significant shift in the center of power of the pharmaceutical industry: of the fifteen largest global firms in 2005, nine were headquartered in the United States, whereas one was in France, two were in Switzerland, and the sole German

firm to make the group came in the fourteenth position. Through the mid-1980s, the balance was rather more evenly distributed: even though only three of the top fifteen firms were based in Germany, two of them – Hoechst and Bayer – held the top two positions (see Tables 1 – 3).

Three snapshots in time of the top fifteen firms ranked by total pharmaceutical sales underscore the shift from Europe to the United States. All of the leading firms expanded international markets in this three-decade period, however, sales figures correlate well with new product innovation. Firms headquartered in the United States moved from the bottom half toward the top of the list between 1974 and the present.

Table 2. Top 15 Pharmaceutical Firms by Sales, 1988[10]

Rank	Company Name	Location	Pharmaceutical sales ($ millions)
1	Merck	U.S.	4,984
2	Glaxo	U.K.	4,213
3	Hoechst	Germany	3,868
4	Bayer	Germany	3,628
5	Ciba-Geigy	Switzerland	3,466
6	American Home Products	U.S.	3,218
7	Sandoz	Switzerland	3,089
8	Takeda	Japan	3,076
9	Eli Lilly	U.S.	2,680
10	Abbott	U.S.	2,599
11	Pfizer	U.S.	2,539
12	Warner Lambert	U.S.	2,509
13	Bristol-Myers	U.S.	2,509
14	Eastman Kodak	U.S.	2,500
15	Roche	Switzerland	2,365

Table 3. Top 15 Pharmaceutical Firms by Sales, 2005[11]

Rank	Company Name	Location	Pharmaceutical sales ($ millions)
1	Pfizer	U.S.	44,280
2	GlaxoSmithKline	U.K.	33,960
3	Sanofi-Aventis	France	32,340
4	Novartis	Switzerland	24,960
5	AstraZeneca	U.K.	23,950
6	Johnson & Johnson	U.S.	22,320
7	Merck	U.S.	22,010
8	Wyeth	U.S.	15,320
9	Bristol-Myers Squibb	U.S.	15,250
10	Eli Lilly	U.S.	14,650
11	Abbott Labs	U.S.	13,990
12	Roche	Switzerland	12,900
13	Amgen	U.S.	12,020
14	Boehringer-Ingelheim	Germany	10,840
15	Takeda	Japan	8,530

In addition to this shift in position for firms based on their headquarters location, another striking feature of these tables is the phenomenal growth in sales for top firms between 1988 and 2005, compared to more modest growth during the 1970s and early 1980s. For many of the top firms, this growth was achieved through mergers and heavy marketing of new products. Yet at least half of the top fifteen companies did not achieve growth through mergers and instead expanded sales significantly based on new product introductions alone. More generally, the nearly ten-fold sales growth between 1988 and 2005 indicates the degree to which pharmaceuticals have become high-demand consumer products. While U.S.-based firms have advantages from their location in the world's largest single market, some non-U.S. firms have done well in this system; three of the top four firms are headquartered in England, France, and Switzerland.

Beyond rank ordering by size, European firms have not kept pace with U.S.-based counterparts in spending on research and development. In the mid-1970s, European pharmaceutical firms (including those in the United Kingdom) accelerated spending from $966 million to $2.4 billion while companies in the United States expanded from $640 million to $1.2 billion. By 1994, however, the top 13 U.S. pharmaceutical firms spent $8.6 billion on R&D while the top European firms combined for $5.8 billion. A decade later, firms in the United States had tripled spending to $27.3 billion while European firms increased more moderately to $9.3 billion. Aggregated pharmaceutical R&D expenditure by top U.S. firms had gone from one-half to triple that of European firms.[12] Are these figures evidence of successful cost-containment across Europe in contrast to a more profligate healthcare system in the United States? Or does the evidence suggest a shift in new product innovation from Europe to the United States?

Table 4. New Chemical Entities by Headquarter Country of Inventing Firm[13]

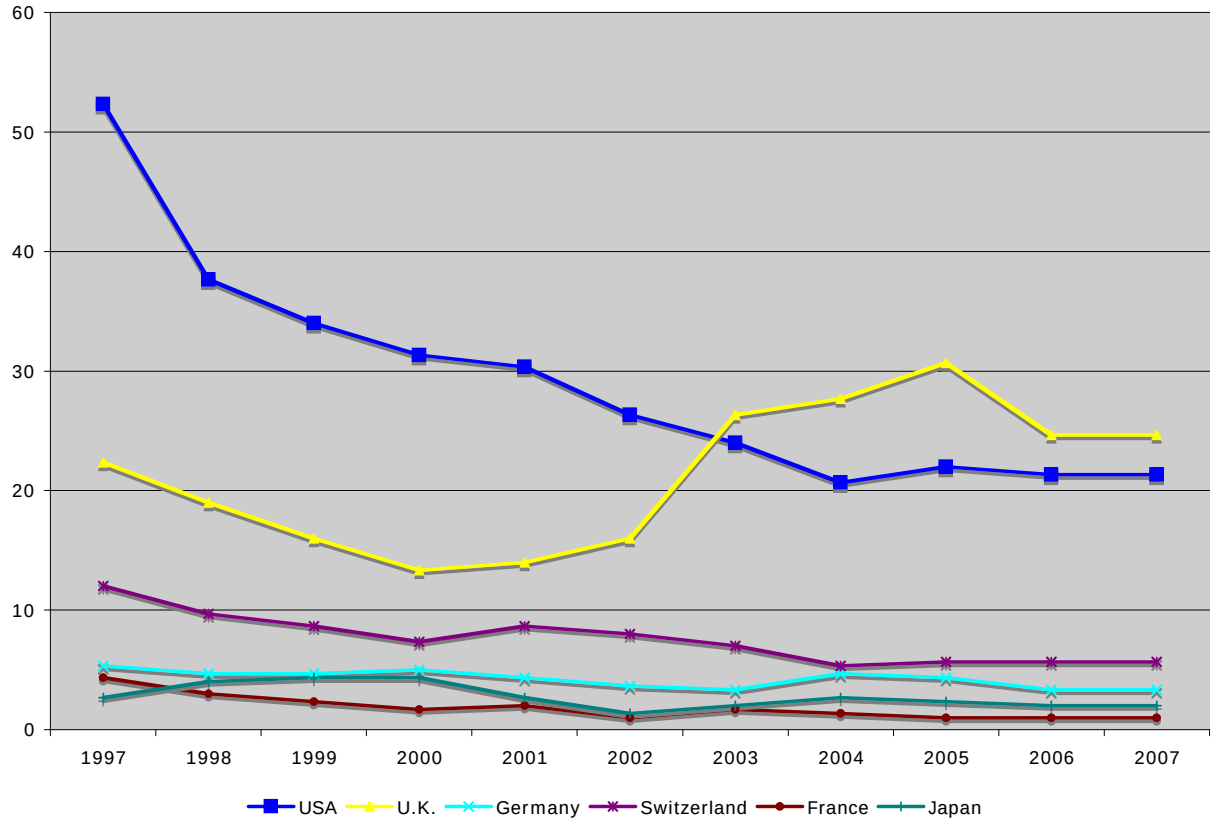
	1961 – 1970		1971 – 1980		1981 – 1990		1991 – 2000	
	NCEs	% Total	NCEs	%Total	NCEs	%Total	NCEs	%Total
USA	209	30	157	31	145	32	75	42
France	172	25	98	19	37	8	10	6
Germany	115	17	96	20	67	15	24	13
Japan	80	12	75	15	130	29	16	9
Switzerland	68	10	53	10	48	11	26	14
U.K.	48	7	29	6	29	6	29	16
Total NCEs	692		508		456		180	

Looking at the market introduction of new chemical entities (NCEs) for all firms not just the largest, we find a relative decline of German and French firms compared to companies in the United States and the United Kingdom (Table 4). In the two decades between 1961 and 1980, firms based on the European continent invented and brought to market over sixty percent of new therapeutic molecules. Of the top ten firms bringing NCEs to market, only two (Johnson & Johnson and Pfizer) were located in the United States, whereas three were in Germany (Hoechst, Boehringer Ingelheim, and Bayer), two were in France (Sanofi, Rhone-Poulenc) and three were

in Switzerland (Sandoz, Ciba-Geigy, and Roche).[14] By the decade beginning in 1991, however, firms in the United States were inventing over forty percent of new drugs and England's relative position improved through mergers that produced GlaxoWellcome, SmithKline Beecham, and AstraZeneca (with a significant Swedish legacy). Germany's relative ranking slipped further after 2001, as Hoechst first merged with Rhone-Poulenc into Aventis in 1999 and then disappeared further with the Sanofi-Aventis merger of 2004. Mergers that created GlaxoSmithKline and Novartis have propelled these companies into the upper echelon of the industry, but from a sector perspective, Europe's pharmaceutical industry, most notably Germany's, dropped out of nearly all rankings of top firms by the mid-2000s.

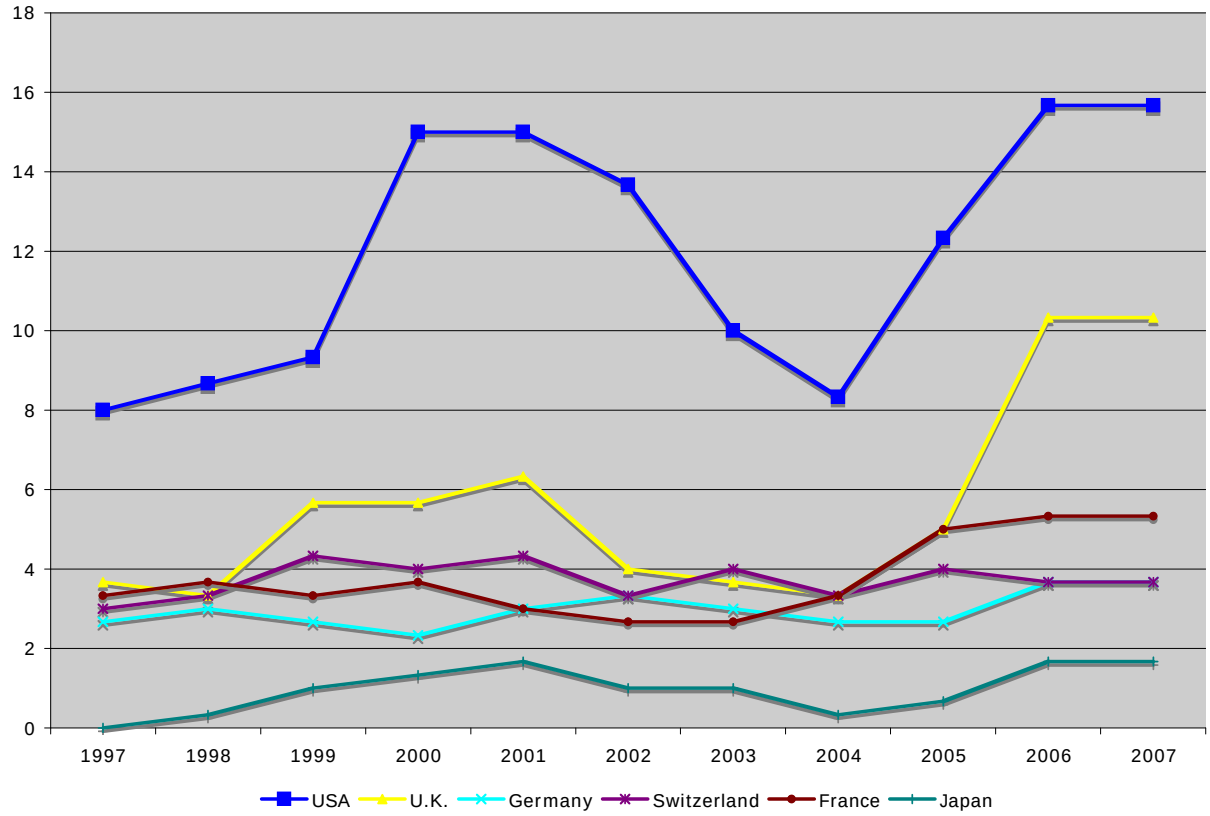
To bring these trends up to the present, I created a new database based on all new drug approvals by the FDA and the European Medicines Evaluation Agency (EMEA) in the eleven years between 1997 and 2007. Launched in 1996, EMEA's approval processes were fully operational in 1997. Duplicate medicines and additional dosage forms were removed from the analysis, leaving just new chemical and biological drugs. Companies were then coded for their national headquarters at the time of the approval.

Figure 1. New Drug Approvals in United States, 1997-2007*



* 3-year moving average

Figure 2. New Drug Approvals in the European Union, 1997-2007*



* 3-year moving average

The graphs in Figures 1 and 2 underscore a longer-term outcome of the shifts in sales and R&D spending since the early 1980s. In the eleven years between 1997 and 2007, firms in the United States nearly forty percent of all FDA approvals and invented slightly over thirty-five percent of all drugs approved by EMEA. Firms in Germany had six percent of all FDA and nine percent of all EMEA approvals, suggesting an orientation toward the European market. British firms, by contrast, had thirty percent of FDA approvals but only seventeen percent of EMEA approvals, signaling their greater participation in the U.S. market.

Even at the very broad level presented here, we see the attraction of the FDA review process and the U.S. market. Overall, prescription drug sales remain strongly concentrated in the United States, Europe, and Japan. In 2007, worldwide pharmaceutical sales of $663.5 billion were dominated by the United States with $205.8 billion, Japan with $59.3 billion, Germany with $32.2 billion, France with $29.6 billion and the United Kingdom with $17.4 billion. Even with a larger population, Europe's share of global pharmaceutical consumption was nearly fifteen percent less than that of the United States (see Table 5, below).

Clinical trials offer a further indication of where the pharmaceutical industry is orienting its activities. While press attention has focused on the outsourcing of clinical trials to developing countries, as of 2008 the vast majority of trials underway were in North America or Europe. Yet with over twice as many clinical trials ongoing in the United States as in the European Union,

firms appear to be running trials in their home countries, creating a virtuous cycle from R&D investment to testing to market approval for firms in the United States. According to a measure of the attractiveness of countries around the world for clinical trials developed by the consulting firm AT Kearney, Germany ranked tenth of fifteen countries, while the U.S. remained the global leader with China, India, and Russia following. Measured by the patient pool, costs, regulatory conditions, availability of expertise, and infrastructure, Germany's high costs, modest patient populations, and challenges of recruiting participation in clinical research put it below the Czech Republic, the United Kingdom, Poland, and Hungary.[15]

Table 5. Pharmaceutical Sales and Clinical Trials[16]

	2007 Pharma Sales ($BN)	% Worldwide Pharma Sales	Clinical Trials Underway	% of Trials Underway
North America	$304.5	45.9%	37,190	58%
Europe	$206.2	31.1%	13,472	21%
Asia, Africa and Australia	$62.2	9.4%	9,797	15%
Japan	$58.5	8.8%	880	1%
Latin America	$32.0	4.5%	3,247	5%

Whereas safety and efficacy regulation were seen as causes for the industry's decline in the 1970s, its subsequent turnaround has been attributed largely to price control policies in Europe and their absence in the United States.[17] New product innovation, sales, and decisions on where to carry out clinical trials together paint a picture of a pharmaceutical industry in decline in Europe relative to the United States, though England, France, and Switzerland remain significant due in part to one or two very large firms in each country. Nevertheless, The United States and Germany remain the two largest western pharmaceutical markets, as measured by percent of GDP spent on prescription drugs.[18]

Reductions in healthcare spending have been difficult to achieve anywhere in the world; as a result, the decline in pharmaceutical sales in Germany has sometimes been hailed as a measure of success in disciplining an unruly system. In February of 2006, the Bundestag passed legislation lowering the "reference price" – the amount that insurers must cover – to the bottom third of existing prices. Patients are responsible for making up the difference for drugs priced above the limit. However, as a commentary in *Nature Biotechnology* noted, "In theory, innovative drugs should be excluded from the mechanism, but in the past, more and more patent-protected drugs were included as they were dubbed 'pseudo-innovative' by the system's oversight bodies."[19]

A range of commentators have also questions about broader implications for the German economy of a decline in its pharmaceutical sector. Quoting an expert from the trade magazine kma, *Deutsche Welle* thus reported in April 2005, "Germany has refused to play catch up and as a result has clearly lost out in importance."[20] An interview with Nikolaus Schweickart, CEO of the specialty chemical and pharmaceutical firm Altana offers an interesting insight into corporate

decisions that lie behind this 'refusal to play catch-up': "In terms of pharmaceuticals strategic conditions, Germany is, in principle, an attractive market. Germans are getting older. There are 80 million 'consumers' here, and the older they get, the more medicine they're going to need." Schweickart blames a structural issue for industry's move out of Germany: "our system, which considers the pharmaceuticals industry and its innovations solely as a cost factor and not as a use factor…is the basic problem."[21] Even the recent merger of Schering and Bayer was greeted with skepticism, with analysts noting that two mid-size German pharmaceutical firms merging would only create the world's 12th largest drug company. "The decline of firms that once made Germany prominent in pharmaceuticals has been breathtakingly rapid. Over the past 10 years, Hoechst, Hexal, Asta Medica, Boehringer Mannheim and BASF's pharmaceutical branch have all changed hands and are now foreign controlled."[22]

These and other reports concerning the status of German and European pharmaceutical manufacturers share the perspective that cost controls alone explain this shift. American patients are thus benefiting with "access to cutting-edge medicines before they are available in Europe."[23] An influential study by the consulting firm Bain & Company, *Addressing the Innovation Divide*, offered three primary advantages for the United States: government support for basic biomedical science, investors' risk tolerance in supporting new companies, and "synergy" between scientists in industry and universities. Bain's analysts concluded that price controls were stifling innovation in Europe. Quantifying results, Bain estimates that Germany lost nearly $5 billion in health value from lowered access to innovative drugs and thousands of "high value added" jobs that were created instead in the United States.[24]

Explaining the shift in pharmaceutical centers of power solely through the economics of drug pricing and mergers, however, misses key aspects of the industry's structure. Firms may be motivated to open sales branches in countries with higher margins, but this does not explain the relative decline of the German and French pharmaceutical industry. While measures of the top fifteen firms may be skewed because German firms did not merge to global scale in the same way as companies in the United Kingdom (GlaxoSmithKline), France (Sanofi-Aventis) or Switzerland (Novartis), smaller firms in the United States (Eli Lilly) and Japan (Takeda) also did not undertake significant mergers to achieve growth. Instead, as the rest of this essay argues, differences in regulatory cultures – notably, responses to a new disease, boundaries to compassionate use, and attention to biomarkers and other aspects of consumer-oriented drug development – provide an important explanatory dimension missing from other analyses. Results presented here focus on the United States and Germany; further work is needed to develop this explanation for changes in other countries, especially France and Japan. The comparison reveals that pharmaceutical firms in Germany operate in a distinctive innovation and regulatory culture characterized by tensions regarding authority and evidence among physicians, industry, and government officials. The German system operated in a collaborative mode that fostered its domestic pharmaceutical industry before the 1980s. Since that time, the predictability of centralized regulation based on a tight regime of quantified clinical trials in the United States

coupled to the emergence of a focus on consumers and their access to drugs ultimately benefited firms operating in that country over their German counterparts.

III. Consumer-Oriented Pharmaceutical Regulation

Although there were some 19th century precedents, government mandates for proof of safety and efficacy primarily were established over the course of the 20th century, especially in the wake of the thalidomide tragedy of the early 1960s.[25] Yet by the early 1980s, concerns were raised in the United States that regulation was preventing beneficial and even life-saving medicines from reaching patients. In effect, a new form of surveillance and regulation emerged based on disease-based interest groups that not only pressure legislative bodies for additional research funding, but also closely monitor both government agencies and industry. Employing the internet and other communication technologies to build their membership and communal identity, these groups significantly impacted the regulatory terrain. In the U.S., patients with HIV-AIDS, breast cancer, and other diseases mobilized to focus research agendas on their illnesses, protest drug prices for life-saving therapies, and demand speedier regulatory review. Policy debates in Europe followed a different direction, with greater attention to prices, equality of access, and protection from dangerous compounds. A shift to new regulatory approaches did not take place to the same degree, likely due to a combination of fewer resources among potential activists and health systems that provided not just drugs, but more comprehensive care. As described below, contrasts between the United States and Germany and other EU countries indicate that a new 'consumer' mode of regulation has taken hold in the United States whereas administrative approaches continue to dominate in Europe.[26]

Responding to a New Disease

When HIV-AIDS began spreading in the early 1980s, patients with the then always-fatal disease began pushing industry and government for new treatments. The disease eventually provoked a crisis in American drug regulation, pitting disease activists against an agency supposedly acting in their interests. As in the United States, the appearance and spread of AIDS posed challenges to the Germany regulatory system. A neo-corporatist sharing of regulatory authority among government officials, the medical profession, and industry, however, prevented people with AIDS from easily locating a physical or administrative site for protest actions. More comprehensive medical care and a less visible and formally structured drug approval process meant that there were comparatively fewer focal points and consequently, fewer demands for access to the regulatory process.

In the United States, groups including the New York Gay Men's Health Crisis, San Francisco's Project Inform, and chapters of the AIDS Coalition To Unleash Power (ACT UP) protested slow drug approval rates and urged faster infusion of "drugs into bodies."[27] Under pressure from these activists and a well-publicized protest at its headquarters, the FDA began to change the drug approval process in an effort to shorten review times. The first anti-AIDS drug AZT (Zidovudine) was distributed to more than 4,000 patients in 1986 and gained marketing

approval after just 107 days of FDA review; this was reported widely as the fastest approval since 1962 for a major therapeutic product.

A year later, the agency issued the first in a series of rules intended to expedite the availability of experimental drugs, known as treatment investigational new drug (treatment IND) regulations. Under these provisions, companies could distribute unapproved medicines to patients with life-threatening diseases, so long as there was a "reasonable basis" for concluding that the drug was effective and would not expose patients in clinical trials to "significant additional risks."[28] Expansion of the treatment IND regulations in 1988 and 1990 made experimental drugs more accessible to AIDS patients, including those not participating in clinical trials.[29] In 1992, the FDA formally adopted a system for "parallel track" review.[30] The parallel track initially provided drugs to AIDS patients who were not taking part in clinical trials. It was later broadened to allow private physicians to prescribe medicines to HIV-positive individuals not yet exhibiting symptoms of full-blown AIDS.[31]

FDA regulations that specified methods for clinical trials and required each new drug application to include data from at least two controlled clinical trials led activists to target these issues as well. In particular, patient groups denounced screening methods, requirements for placebo use, and restrictions on trial participants.[32] Activists thus brought public scrutiny and wider input to arguments about the number of participants necessary to prove drug safety and efficacy, access to data, how active a role patients could play, and more broadly, the extent to which clinical trials should match complex, often contradictory, 'real world' conditions.

In a further response to activists' criticisms, the FDA began approving drugs based on surrogate endpoints, formalized in the 1992 "accelerated approval guidelines."[33] Rather than rely exclusively on measurable long-term survival, the FDA accepted changes in T-cell counts, measures of the amount of virus present in the blood (the viral load), and other data as a surrogate for overall health. Partly due to these changes, FDA review times declined rapidly in the 1990s.[34] A bounded set of reforms thus made drugs available to patients outside of clinical trials and policy changes loosened the structure of clinical trials themselves. As a result, companies could more easily recruit patients and potential new drugs moved from the laboratory to the clinic more rapidly than in the past.

Whereas American activists protested the FDA, German AIDS patients found it difficult to articulate a stance as outsiders demanding representation in regulatory decisions.[35] Instead, concerned individuals—mostly gay men—mobilized volunteers in prevention and education efforts. They also provided direct assistance for patients in advanced stages of the disease. Deutsche AIDS-Hilfe, a publicly supported organization, was formed in Berlin in 1983 and soon established chapters in cities across West Germany. The group subsequently gained a monopoly position to represent AIDS patients with government officials.[36] As a quasi-public administration, the organization rarely adopted confrontational techniques to bring about changes in public policy. Formation of a national AIDS advisory council, the AIDS-Beirat, likewise produced few policy changes concerning drug regulation. Supported by a federal government "eager to establish one peak body with whom they can deal," the AIDS-Beirat worked within

established channels and focused its attention on public education, insurance benefits, and daily assistance for very sick AIDS patients.[37] More confrontational organizations such as ACT-UP made their presence felt, but failed to attract much popular support.

Patients and activists generally agreed with government officials that the 1976 Drug Law already accounted for contingencies associated with the emergence of a new and deadly disease. Responding to policy changes in the United States, the Federal Health Ministry (BGA) in 1991 issued official recommendations concerning the pharmacological and toxicological tests it required prior to initiating clinical trials for AIDS drugs.[38] Government officials advised scientists to avoid duplicate pharmacology tests and reduce the time spent determining toxicity in animals. Official pronouncements of this type indicate how discussion of AIDS and access to medicines was framed in terms of technical details relating to drug testing. Access to test results, however, remained limited to the drug company, physicians conducting clinical trials, and government officials. Since well-controlled boundaries distinguished between experts and patients, drug testing did not become a site for debates about representation or access to medicines.

In a second development of potential significance for German regulatory politics, failure to test the nation's blood supply allowed HIV to spread among hemophiliacs and other recipients of blood transfusions in the late 1980s. The public outcry and political uproar that followed ultimately led to the split of the BGA into three successor institutes in 1994.[39] Just as in the past, however, the incident did not activate possible lines of cleavage between insiders and external critics. Decision-making procedures at the newly-formed Bundesinstitut für Arzneimittel- und Medizinprodukte (BfArM) thus mimicked previous BGA approaches. Even though the spread of AIDS and concerns about drug approval rates were important features in German politics of the 1980s and early 1990s, comparatively little pressure was put on the network of physicians, regulators, and the pharmaceutical industry.

Compassionate Use and Underserved Patients

In recent years, the compassionate use of pharmaceuticals still in various stages of pre-market testing has engaged patient groups, industry, and government agencies in ways that further illustrate the differences in regulatory approaches followed by the United States and Europe. Patients with terminal diseases have long occupied a special status and despite stronger regulatory controls implemented over the course of the 20th century, physicians have retained the right to prescribe medicines for off-label uses. Nevertheless, until a drug has an initial FDA or EMEA approval it is banned from the market with the special exception of the clinical trial. Changes to FDA policies in the late 1980s and early 1990s laid the basis for patients with HIV/AIDS to obtain medicines under treatment IND regulations and the parallel track system. Nevertheless, many patients with other life-threatening diseases continued to fall outside the health status defined by sponsor companies for their experimental drugs.

For companies required by law to report and investigate any adverse reactions or fatalities related to their drugs, compassionate use programs pose a challenge. To deny an unapproved

drug to a dying patient appears cruel. But firms are understandably nervous that if a patient dies while taking a still-experimental therapy, it can be difficult to differentiate the natural course of disease from an adverse reaction to the treatment.

Citing several tragic cases of terminally ill patients who failed to qualify for clinical trials of new anti-cancer agents due to their advanced disease, the Abigail Alliance (begun by Frank Burroughs and named for his deceased daughter) filed a lawsuit heard in D.C. district court in 2005. Specifically, the Alliance sought to make available any drug that had cleared phase I trials (which collect data about a chemical's pharmacological properties in small numbers of healthy subjects; they generally do not determine dosage or efficacy in patients with the disease). In May 2006, the D.C. district court upheld the Abigail Alliance argument on appeal, with the majority finding that a terminally ill patient had the fundamental right to choose medication, even though the safety and efficacy of the therapy may be under question and the FDA had not yet reviewed the drug.[40] A major feature of the subsequent firestorm of commentary was the dilemma this posed for structured clinical trials. In the United States it is now widely held that the production of information about drugs requires large, double-blinded, placebo-controlled studies. In this framework, the individual is served best by statistical analysis of large populations. Medical authorities and the industry worried that access to medicines outside of clinical trials would undermine incentives for patients to volunteer as subjects. When the D.C. district court heard the case *en banc* in 2007, justices reversed the previous decision, finding that all phases of testing are necessary and that the "government has a rational basis for ensuring that there is a scientifically and medically acceptable level of knowledge about the risks and benefits" of new drugs.[41]

In Europe, access to drugs prior to completion of testing and regulatory review is explicitly the responsibility of physicians and pharmacists, with a more diminished role for government agencies. As a consequence, the issue does not feature as prominently in legal circles or media coverage of pharmaceutical regulation. In Germany, for example, the prescribing physician performs an individual benefit-risk analysis and the pharmacy checks whether the drug qualifies for commerce, specifically whether it is defined as "hazardous" under §5 of the *Arzneimittelgesetz*. In contrast to a procedural approach in the United States that requires physicians to negotiate with FDA to make a treatment available, in Germany a dialogue between physician and pharmacist draws on professional norms for the risk calculus in the individual case. Driven in part by the emergence of alliances for patients with rare and fatal diseases across Europe, the EU currently is developing new legislation for compassionate use programs. A guideline issued by EMEA in July 2007 emphasized that compassionate use should not "slow down the implementation or continuation of clinical trials," but gave countries space to define programs in line with their medical norms.[42] To date, EMEA has not issued a final harmonized ruling on compassionate use, leaving member countries to base procedures largely on their individual histories.

As an issue that closely followed the dynamics around HIV/AIDS, access to drugs still in clinical trials for patients with other life-threatening diseases has been an area of regulatory

contention and change in the United States and comparatively subdued harmonization efforts in Europe. Physicians and pharmacists act as expert gatekeepers in most European countries whereas FDA officials are thrust into this role in the United States. One outcome of this difference is a greater tension in the United States than in Europe between the individual patient and large "n" populations needed for clinical trials. At the same time, policy changes have involved public debate and formal legal decisions resulting in a reaffirmation of the importance of clinical trials as a predictable and managed part of the drug development process. The less politicized local decision concerning a patient's access to drugs through compassionate use programs in Europe ironically may be fostering uncertainty for firms developing and advancing new pharmaceuticals.

Personalized Medicine

The concept of consumer oriented or personalized medicine has attracted wide attention in recent years. Regulators in both the United States and in Europe are at present seeking to identify and validate biological markers that can serve as surrogate measures for clinical outcomes. To date, surrogate endpoints are proving contentious, with relatively little international agreement on which measures to use and how to prove they correspond rigorously to actual health outcomes. While the area is in flux at present and likely to change in coming years, certain trends have emerged. First, whereas the FDA and EMEA are making similar approval decisions based on surrogate measures, the tier of reimbursement and clinical efficacy decisions increasingly found across Europe pose additional challenges to manufacturers. For example, both FDA and EMEA approved Avastin for metastatic breast cancer based on clinical data showing a prolonged progression-free survival, but not a statistically better overall survival. With a cost that can reach up to $100,000 per year, Avastin has raised some concern in the United States; its use in Europe is even more contested.[43] Thus the U.K. National Institute for Clinical Excellence terminated the review of Avastin in June 2008, making it unavailable through the National Health Service to women with breast cancer.[44]

Second, whereas new partnerships have been formed between regulators and industry to foster the development and validation of biomarkers in the United States, in many European countries, and at the EU-level, these arrangements are structured quite differently. The critical path initiative in the United States originated with a 2004 FDA white paper that drew attention to declining new drug applications and called for new approaches to clinical testing, notably through the use of surrogate endpoints and validated biomarkers.[45] Since that time, the Critical Path Institute, a new non-profit organization with a mandate to foster collaboration among FDA, industry, and academia, has been working to validate new biomarkers.[46] In 2006, FDA announced 76 specific issues for collaborative research and action. Regular updates and new initiatives within the critical path framework are posted regularly to the FDA website.[47] Nevertheless, commentators have noted that FDA's move toward personalized medicine is gradual: "even in cases where a specific diagnostic test was used as a criterion for enrolling drug-trial participants, the agency has only infrequently required doctors to perform the test before

prescribing the drug."[48] At the EU level, a major initiative launched in early 2008, the Innovative Medicines Initiative, plans to spend some $3 billion in the next five years. While it has been compared to the Critical Path initiative, it is likely to spend far more to support research in areas such as brain disorders and metabolic disease than for biomarker development and validation or for new clinical trial methods.[49] National regulatory agencies in Europe are also exploring biomarkers, though with different degrees of urgency. In Germany, for example, BfArM convened several expert assessments and conferences. At a meeting in June 2007, BfArM put the onus on industry and academic researchers to change the design of clinical trials:

> To date, genetic biomarkers have rarely been incorporated in well-controlled late phases of clinical trials for the purpose of a proactive patient selection or patient stratification. Application of pharmacogenetics-based diagnostics in therapeutic decisions would be facilitated if pharmacogenetic analyses were already included in the clinical studies during the development of drugs, but currently this diagnostic approach is still far from being applied in general clinical practice.[50]

While the FDA is taking a proactive role in seeking to reshape clinical practice in the United States, at this stage it appears that in Germany and other European countries, agencies are taking a more passive role and expect the medical community to arrive at a consensus on the use of biomarkers to determine drug efficacy.

Third, at a broad conceptual level, finding a fit between protection of "the patient" and providing information to "consumers" is being conceptualized differently in the United States and Europe. Writing in the *New England Journal of Medicine*, U.S. Senate Majority Leader William Frist described a fictional patient and the overall healthcare system in the year 2015 in a manner that succinctly envisioned a personalized therapeutic approach:

> Rodney does an excellent job with his self-care. He takes a single pill each day that is a combination of a low dose of aspirin, an angiotensin-converting-enzyme (ACE) inhibitor, a cholesterol-lowering medication, and a medication to manage his blood sugar. … The focus of the 21st century health care system must be the patient. During the next decade, the practice of medicine will change dramatically through genetically based diagnostic tests and personalized, targeted pharmacologic treatments.[51]

By contrast, discussions in Europe appear to be more technical in nature with a focus on realizing healthcare cost savings from new testing approaches. Interviewed by the journal *Personalized Medicine*, Dolores Ibarreta of the Institute for Prospective Technological Studies at the European Commission Joint Research Center, explained:

> In the specific context of personalized medicine, we are looking at barriers for development and clinical implementation in Europe. … We are concentrating on IP issues and data protection requirements, as these are issues with a high policy profile. … We are also looking at how cost–effectiveness of pharmacogenetic testing is being ensured in Europe and what could be done to promote it.[52]

Tensions emerging in the United States between making health care responsive to consumers while protecting patients and ensuring they have treatment and care are notably less pronounced

in Europe. By contrast, Europe continues to take access for granted – either therapies are effective and affordable and therefore universally available, or they are neither – and has correspondingly less policy debate about the emergence of personalized medicine.

IV. Conclusion: The Interface of Innovation and Regulation

Since 1980 and at a rate that accelerated in the 1990s, the United States became the leading worldwide location for pharmaceutical research, clinical testing, and marketing. The "pharmacy to the world," once located at the intersection of Germany, Switzerland, and France, today is found in the United States. Studies of the industry have attributed this sustained competitive advantage to a variety of factors, including U.S. intellectual property policies, funding for biomedical research through the National Institutes of Health, the absence of government controls on drug prices, and the availability of venture capital and other factors that fostered the growth of the biotechnology industry.[53] This essay adds the regulation of clinical trials and its structured reform as a critical additional aspect to understanding strategy and operation of the pharmaceutical industry.

Government regulation of the pharmaceutical market is revealing of a country's innovation concept at a specific historical moment; intriguingly, regulations also shed light on enduring cultural differences between nations. The U.S. Congress increased FDA's authority and mandated formal rules for drug evaluation in response to precipitating events, notably cases of widespread adverse drug reactions. Historically, legislative interventions in the United States were predicated on the notion that patients must be protected by the state from the worst ravages of free-market capitalism. Congress and the FDA expected government control over pre-market testing to protect patients otherwise open to abuses by industry and the medical profession. In the 1980s and 1990s, however, patients represented by disease-based organizations agitated for greater access to drugs and speedier approvals. At the same time, critics warned that the country's competitive standing depended on the pharmaceutical and biotech sectors. A strict boundary between testing and marketing – established by legislative initiatives and implemented rigorously by FDA officials – then was softened to allow for greater access to new medicines. Regulation of pharmaceuticals in the United States has followed an overall progression from medical profession to the state to a new consumer/patient oversight model.

In Germany, by contrast, the medical profession exercised a near-monopoly over constructions of "the patient" and drug laws codified existing power-sharing arrangements. Instead of the state claiming authority over pre-market testing, it acted as one member of a network overseeing pharmaceutical drugs. A flexible boundary between testing and market was predicated on informal trial protocols, a structured system for collecting reports of adverse reactions, and compromises among organized interests and government officials. Because the medical profession successfully maintained and even expanded its authority to speak for the patient in the post-World War II era, few activist groups or other disease-based organizations mobilized to change the regulatory system. The drug approval process thus only rarely became a significant site for debates over national competitiveness or industry innovation. Nevertheless,

Germany too has seen different waves of regulatory style, from physicians to a networked approach that incorporates the state, select disease-based organizations, and the medical profession.

The comparative perspectives developed in this essay suggest that despite recent convergences in government efforts to stimulate and steer innovation, for example through support for small biotech ventures, national regulatory differences influence the competitive status of the pharmaceutical sector. In contrast to the argument that it is German and European healthcare cost containment that undermined the pharmaceutical sector, this essay suggests instead that regulation also plays a role in the success and failure of industry. In fact, the emergence of a consumer/patient regulatory mode in the United States has driven increased use of prescription drugs. While this comes at high financial cost and stress on government regulators, it offers the benefits of avoiding painful cost vs. life decisions as faced regularly in England, or undermining a significant industry sector as in Germany. At the same time, the consumer mode that has emerged in the United States has proven easy to manipulate for industry, as in the cases of corporate-financed organizations claiming to be self-organized by patients. It has also driven a focus on disease prevalent in wealthy countries, to the detriment of research into HIV-AIDS, malaria, and other ailments prevalent in the developing world.

A combination of public attention to drug prices, health concerns from product withdrawals due to adverse reactions, and criticisms of the failure to deliver medicines to patients in developing countries pose significant challenges to industry and regulators. Research on the interplay of pharmaceutical innovation and regulation presented here suggests that significant change in the blockbuster model followed by most pharmaceutical companies may not happen as quickly as critics would like. An open question is whether the current “pharmacy to the world” of the United States may soon loose ground to competitors from developing countries. As Indian and Chinese firms that started in the generics business integrate upstream into the invention and testing of new molecules, they may become the next generation of competitors to the current top-ranking firms. Finally, the emergence of a consumer model of regulation poses a number of critical unresolved questions about the longer-term role of government, industry, the medical profession, and citizens. The era of paternalistic medicine has passed, but the notion that patients can act as consumers and make appropriate decisions concerning medical treatment poses countervailing risks of its own. A better accommodation among key players needs to be struck to foster safe use of pharmaceuticals. The precise form of this accommodation will necessarily vary from one country to the next, which holds out the possibility for additional policy learning from future cross-national comparisons.

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