Chapter 2: Institutions

(version 5.1)

Chapter 1 of this book examined the most prominent of the infectious diseases that are currently rampant in developing countries. A recurring theme was the need to generate new vaccines and medicines that would reduce the burdens caused by those diseases – and then to make high-quality versions of those vaccines and medicines accessible to the people who could benefit from them. How we might do that is the principal focus of Part II of this book. The present chapter provides background for Part II by sketching the machinery currently used by governments and nongovernmental organizations to manage the development and distribution of new pharmaceutical products.

A. Developed-Country Governments

Drugs differ from most products in several ways. First, they are unusually important. They are capable – sometimes uniquely capable – of preventing or curing potentially fatal or debilitating illnesses. Society thus has a larger stake in fostering their production than it does with respect to most goods and services. Next, they are unusually dangerous. The magnitude of their potential benefits is matched by the magnitude of their potential harms. Moreover, prediction of which drugs will be harmful and to whom is difficult. Typically, ordinary consumers are incapable of making such judgments. Finally, inventing new drugs is more expensive and risky than inventing most products. The hazard that they will be created in suboptimal numbers is thus severe. These features, in combination, help explain why most governments in the world have long devoted more attention to drugs than to any other product.

You might expect that, in each country, a single government agency would conduct or coordinate the management of drugs. Remarkably, in no country is that true. Instead, the task is subdivided, and the separate dimensions are handled by different systems. Most countries divide the job into three portfolios: the task of stimulating research and development; the task of ensuring that the drugs distributed to patients are safe and effective; and the task of ensuring that the people who need those drugs can get them. For simplicity, we will refer to these functions as the incentive function, the quality function, and the access function.

This section summarizes the ways in which each of these functions is currently handled by the governments of most developed countries. For reasons that will become apparent, we will devote disproportionate attention to the United States, but will also take note of the modest respects in which the systems used in other developed countries differ.

1. Incentives

Understanding the incentive function requires a brief foray into intellectual-property theory. This is well-mapped territory, so we will traverse it quickly.

Economists have identified an important category of products that they refer to as "public goods." Things of this sort have two related characteristics. First, they are nonrivalrous. In other words, they are not "used up" through consumption. As a result, an

unlimited (or nearly unlimited) number of people can benefit from them. Second, they are "nonexcludable." In other words, once they have been made available to one person, it is impossible (or very difficult) to prevent other people from gaining access to them without permission. Goods and services that have these linked features include navigational aids (such as lighthouses), transportation facilities (such as roads), national defense, and reproducible art.

Most public goods have large social benefits – because they can be enjoyed so widely. However, unless governments intervene in some way to promote them, public goods tend to be produced in inefficiently low quantities. The reason is that private parties considering producing them quickly realize that they will have difficulty charging people for access to them.[1] The classic illustration: a person or firm considering building a lighthouse to warn ships to avoid a dangerous reef soon realizes the impossibility of collecting a fee from all of the mariners who would benefit from the lighthouse – and so abandons the venture.[2]

The hazard that public goods will be underproduced is exacerbated by some circumstances and mitigated by others. Exacerbating circumstances include: high "up front" costs of creating the good in question; uncertainty concerning whether an effort to create it will succeed (which discourages risk-averse potential creators); and the ease with which embodiments of it may be replicated. Mitigating circumstances include: industry customs or lead-time advantages that enable the creators of public goods to recover some or all of their up-front costs; network externalities (which tend to raise barriers to entry and thus increase the ability of the producers of the good to recoup their costs); opportunities for increasing excludability through self-help strategies (such as secrecy or encryption); and non-pecuniary motivations for creating the good at issue (for example, fame, reputation, academic tenure, scientists' pursuit of truth, or the pleasure of participating in collaborative creative communities).[3]

Against this backdrop, the reasons why governments must intervene to encourage the creation of new drugs should be apparent. Pharmaceutical innovations exhibit both of the characteristics that define public goods. Of course, the pills, capsules, or injections that

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[1] See Jeremy Bentham, *A Manual of Political Economy* (New York: G.P. Putnam, 1839); John Stuart Mill, *Principles of Political Economy* 5th ed. (London: Longmans, Green & Co., 1909), 932-33; A.C. Pigou, *The Economics of Welfare*, 2d ed. (London: Macmillan & Co., 1924); and J. G. Head, "Public Goods and Public Policy," *Public Finance* 17 (1962): 197-221.

[2] Ronald Coase once argued (in contrarian fashion) that private parties had been able to construct lighthouses and operate them at a profit without state aid. See "The Lighthouse in Economics," *Journal of Law and Economics* 17 (1974): 357-76. It turns out, however, that he misinterpreted the relevant history. See David E. Van Zandt, "The Lessons of the Lighthouse: 'Government' or 'Private' Provision of Goods," *Journal of Legal Studies* 22 (1993): 47-72; and Steven Shavell, "The History of Lighthouses as Public Goods" (unpublished paper, February 1996).

[3] For examinations of the economics of particular public goods that emphasize one or another of these factors, see Yochai Benkler, "Coase's Penguin, or, Linux and the Nature of the Firm," *Yale L. J.* 112 (2002); *The Wealth of Networks: How Social Production Transforms Markets and Freedom* (New Haven: Yale University Pres, 2006); Stephen Breyer, "The Uneasy Case for Copyright: A Study of Copyright in Books, Photocopies, and Computer Programs," *Harvard Law Review* 84 (1970); John M. Golden, "Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System," *Emory Law Journal* 50 (2001); Amy Kapczynski, "Order without Intellectual Property Law: Open Science in Influenza," *Cornell Law Review* 102 (2017); Arti K. Rai, "Regulating Scientific Research: Intellectual Property Rights and the Norms of Science," *Northwestern University Law Review* 94 (1999); Kal Raustiala and Chris Sprigman, "The Piracy Paradox Revisited," *Stanford Law Review* (2009).; Ferrell 1995.

embody those innovations are rivalrous and excludable; each can only be consumed by one patient. But the innovations themselves are both nonrivalrous and nonexcludable. The benefits arising out of a discovery of the medicinal benefits of a particular compound can be enjoyed by an unlimited number of persons, and once a drug containing that compound is provided to one patient, the discoverer will have great difficulty preventing competitors from replicating it – and thus will have trouble charging other patients for access to the discovery.

In addition, all of the circumstances that exacerbate the hazard of underproduction and few of the circumstances that mitigate it apply to pharmaceutical innovations. The costs of generating new drugs are extraordinarily high and the probability that any given research project will succeed is both distressingly low and apparently diminishing. The ease with which most pharmaceutical innovations can be deciphered and copied, and the low marginal costs of producing copies, increase the likelihood that innovators will be unable to recover their up-front costs. For much the same reason, the lead time enjoyed by the creator of new drug is usually short. Increasing excludability through self-help is typically impracticable; pills can't be encrypted. And most potential innovators in the pharmaceutical field are relatively insensitive to non-pecuniary rewards.

There are some exceptions to these generalizations. For example, reverse engineering and replicating the new "biologics" is harder than it is for "small molecules"; vaccines (as we have seen) do exhibit network externalities; and some of the academic researchers who are key contributors to the chain of innovations that lead to new drugs are motivated by nonmonetary rewards. We will explore in Part II ways in which we might capitalize on each of these features. But it must be conceded at the outset that they pale in importance when compared to the conditions that threaten innovation.

There are five mechanisms that governments commonly employ to offset the risk that public goods will be produced in less-than-optimal quantities. First, governments sometimes produce public goods themselves. Classic examples are lighthouses, roads, and national defense. Second, governments often subsidize private parties who commit to producing public goods. The grants issued by many European governments to filmmakers (especially first-time filmmakers and those engaged in unconventional projects) are illustrative. Third, governments sometimes promise to award prizes to successful producers of particular types of public goods. For example, the discovery of a method for measuring longitude was successfully incentivized in this way. Fourth, governments can increase the financial returns available to the first producers of a public good by suppressing competition in the manufacture and sale of embodiments of that good. Copyright law is the premier example. Finally, governments sometimes increase the "excludability" of public goods by penalizing activities that corrode self-help measures adopted by innovators. Examples include trade-secret law and criminal penalties for trafficking in technologies that circumvent technological protection measures.[4]

When trying to foster innovation with respect to pharmaceutical products, the government of the United States currently relies primarily on a combination of the second and fourth of these strategies. The principal manifestation of the second strategy consists of the

[4] A more detailed exploration of these five options may be found in William W. Fisher, III, *Promises to Keep: Technology, Law, and the Future of Entertainment* (Stanford University Press, 2004)., chapter 6.

grants issued by the National Institutes of Health (NIH) to private parties (typically universities) to support research on topics that can reveal opportunities for new pharmaceutical products. The NIH currently spends roughly $31 billion per year on such "extramural" research (in addition to roughly $4 billion on "intramural" research) – much more than any other nation.[5] A secondary but still substantial manifestation of this strategy consists of the various ways in which the federal government subsidizes the education of scientists, who, upon completing their degrees and fellowships, go to work for pharmaceutical firms.

The other way in which the government seeks to stimulate pharmaceutical innovation consists of suppressing competition in the manufacture and sale of innovative products. The best known of the mechanisms it employs for this purpose is the patent system. In brief, the inventor of a new and nonobvious drug who promptly files a patent application that discloses enough information to enable other chemists to practice her invention is granted a patent that enables her to prevent competitors from making or selling identical or equivalent products for 20 years following the date of the patent application. The duration of protection generated by such a patent is not as great is it might appear. To avoid running afoul of the so-called statutory bars and thereby forfeiting her rights, the inventor is obliged to file for patent protection soon after discovery of the utility of the compound at issue. Typically, the inventor (or, in the usual case, the company for whom she works) must then devote several years to preclinical research and clinical trials, and then await the completion of FDA review (more on this shortly). The resultant reduction of the effective duration of market exclusivity is partly offset by provisions of the Hatch-Waxman Act, which enable the patentee to obtain up to 5 years of extension of the patent term for half of the period devoted to clinical trials and all of the period consumed by the FDA approval process. But even after these adjustments, the patent is likely to expire roughly 12 years after the drug is first marketed. In rare cases, such patents expire even before the products are launched.

In theory, innovators are able to supplement the patents they obtain on new products (so-called "composition of matter" patents) with patents on particular uses of those drugs. If (as is common) the innovators discover new medicinal uses of their creations after they first apply for product patents, they can apply for and obtain so-called "new-use" patents that could extend substantially their terms of protection. In practice, however, the difficulty of enforcing such patents sharply limits their value.[6]

Much more important than new-use patents are the protections against competition that innovators are now able to obtain, not through the patent system, but through so-called "exclusivity" rules, which forbid the FDA to approve, for prescribed periods of time, drugs that would compete with pioneers. Such rules come in various shapes and sizes: 7 years of market exclusivity[7] for "orphan drugs" (drugs that address diseases that affect fewer than

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[5] See National Institutes of Health, Budget, https://www.nih.gov/about-nih/what-we-do/budget. A breakdown of the magnitudes of the grants that NIH devotes to each category of disease is available at https://report.nih.gov/categorical_spending.aspx.

[6] See Rebecca S. Eisenberg, "The Role of the Fda in Innovation Policy," *Michigan Telecommunications & Technology Law Review* 13 (2007).

[7] The terms "data exclusivity" and "market exclusivity" are protean, but roughly speaking the difference between them is that data-exclusivity rules forbid the FDA to accept an application that relies upon safety or efficacy studies conducted by the beneficiary of the exclusivity, whereas market-exclusivity rules forbid the FDA to

200,000 patients in the United States); 5 years of data exclusivity for new chemical entities (NCEs); 3 years of data exclusivity for modifications of existing drugs significant enough to require new clinical trials; an additional 6 months of market exclusivity for on-patent drugs that have been tested (at the FDA's request) for efficacy on children;[8] an additional 5 years of market exclusivity for new antibiotic agents; and, last but not least, 4 years of data exclusivity plus an additional 8 years of market exclusivity for biologics.[9]

Sometimes, these various legal regimes are redundant. For example, the five-year data-exclusivity protection for a pioneering small molecule that enjoys twelve years of useful patent protection is largely superfluous. But in many instances the regimes are complementary. Examples: some NCEs are not patentable; effective patent protection sometimes lasts for less than 5 years; and the ability to bring a patent-infringement suit is a less reliable and more expensive source of protection than a denial of FDA approval to a competitor.

In combination, this set of regimes is highly effective in suppressing competition for the large majority of new drugs for roughly a decade. Illuminating data concerning the impediments that these rules create to generic entry and the resultant ability of innovators to maintain high prices has been gathered and analyzed by Frank Lichtenberg and Gautier Duflos.[10] Relying on a data set encompassing "virtually all prescription drugs sold during the period 2000-2004 in the United States," they show that: mean generic market share remains low until 12 years after a pioneer first enters a market, then increases sharply; prices for drugs rise gradually between entry and year 12, then begin to decline; advertising expenditures by the innovator rise sharply between entry and year 12, then decline; and, perhaps most surprisingly, the total number of prescriptions (pioneer + generics) remains relatively constant between year 12 and year 16 despite the diminution in price. (The principal explanation for the last-mentioned effect seems to be the reduction in advertising and the distribution of promotional

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approve a drug that will compete with a drug developed by the beneficiary of the exclusivity. In most circumstances, rules of the two types give rise to comparable levels of protection, because the cost of conducting the clinical trials necessary to produce and then submit to the FDA a new body of data concerning safety and efficacy is prohibitive.

[8] See GAO, Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act (2007), available at http://www.gao.gov/assets/260/257925.pdf. This 6-month extension is commonly referred to as "pediatric exclusivity." For an assessment of its economic value, see Jennifer S. Li, "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program," JAMA 297, No. 5 (1997).

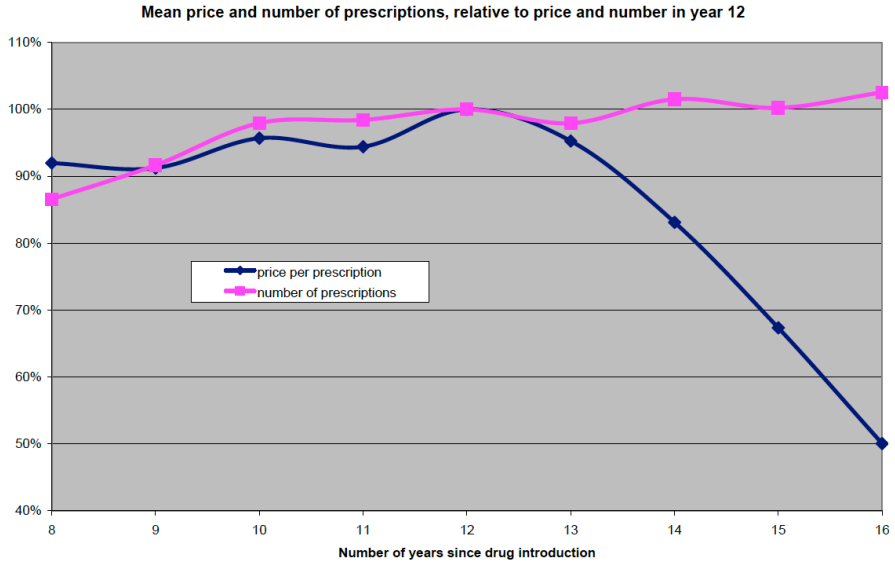
[9] See Letter to FDA Commissioner Hamburg from several generic manufacturers, January 20, 2011, available at http://www.hpm.com/pdf/generics%20biosimilars%20letter.pdf.

[10] See Frank R. Lichtenberg and Gautier Duflos, "The Effect of Patent Expiration on U.S. Drug Prices, Marketing, and Utilization by the Public," *Manhattan Institute for Policy Research* (2009), http://www.manhattan-institute.org/html/mpr_11.htm. Other studies generating results that are roughly consistent with these findings include: Ernst R. Berndt and Joseph P. Newhouse, "Pricing and Reimbursement in U.S. Pharmaceutical Markets," in *Oxford Handbook on the Economics of the Pharmaceutical Industry*, ed. Patricia M. Danzon and Sean Nicholson (Oxford University Press, 2012); Patricia Danzon and Michael Furukawa, "Competition in Generic Pharmaceutical Markets: Cross-National Evidence," in *Petrie-Flom Drugs Conference* (2009); Maxwell R. Morgan, "Regulation of Innovation under Follow-on Biologics Legislation: Fda Exclusivity as an Efficient Incentive Mechanism," *Columbia Science and Technology Law Review* 11 (2010); F.M. Scherer, "The Pharmaceutical Industry -- Prices and Progress," *New England Journal of Medicine* 351, no. 9 (2004).

free samples by the pioneer.) Details concerning the most germane of these trends are provided in the following graphs:[11]

Figure 1

Figure 2



The substantial period of time in which, on average, pharmaceutical firms are shielded against competition (and thus able to charge high prices) enables them to earn generous profits – some of which they then reinvest in research designed to generate new drugs. How much? We don't know for sure, in large part because the firms guard the relevant data fiercely. Some data points: The Congressional Budget Office has estimated that the ratio between the

[11] Both graphs have been taken from Frank R. Lichtenberg and Gautier Duflos, "Does Patent Protection Restrict U.S. Drug Use? The Impact of Patent Expiration on U.S. Drug Prices, Marketing, and Utilization," in *Petrie Flom Dugs Conference* (2009). The same graphs appear (in slightly less useful form) in "The Effect of Patent Expiration on U.S. Drug Prices, Marketing, and Utilization by the Public". 5-6.

amount the firms spend on R&D and their total sales ranges from 8% to 19%.[12] (Michael Scherer shows that the percentage reinvested each year varies with the prices of drugs.[13]) The National Science Foundation estimated some time ago that a total of roughly $39 billion is spent each year on research and development by US pharmaceutical firms.[14] A group of scholars led by John-Arne Rottingen estimated that, in 2008, total annual investment on health-related investment in the United States was $119 billion (in purchasing power adjusted dollars), of which roughly 66% ($78 billion) came from the private sector, 26% ($31 billion) came from government, and 8% ($10 billion) came from other sources (educational institutions [excluding funds derived from government grants], nonprofit organizations, and investments from abroad).[15] Of these various estimates of private investment, that of the Rottingen team is probably the most reliable – and we will continue to rely on their article for other data. But the divergence among the estimates suggests how little we truly know.

To summarize, the principal sources of funding for pharmaceutical research in the United States are roughly $35 billion annually by the NIH (10% intramural and 90% extramural) and *very* roughly $80 billion spent by pharmaceutical firms. The latter sum represents a subset of the profits earned by those firms from sales of their existing products, profits that, in turn, are enabled by a combination of legal regimes that curtail competition in the manufacture and distribution of new and improved drugs.

The stages of the pharmaceutical development process to which these various sums are devoted differ. Broadly speaking, primary research is funded primarily by public money, while applied research and clinical testing are funded primarily by private money.

Analogous incentives can be found elsewhere. All other high-income countries have patent laws that are very similar (in pertinent respects) to US patent law, and most have roughly similar data-exclusivity rules. In addition, the governments of most of the high-income countries subsidize research in much the same way that the NIH does in the US.

No country approaches the *total* expenditures by the United States: $115 billion. As of 2009, the next three countries in total annual expenditures were Japan ($18 billion), Germany ($13 billion), and the United Kingdom ($12 billion). (The disproportionate role currently played by the United States in pharmaceutical research is the principal reason why we are devoting some much attention to the machinery in place there.). However, as Figure 3 shows, in terms of the *percentage* of its gross domestic product that each country spends on health-related GDP, the United States is less of an outlier.

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[12] See Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," (2006).

[13] F.M. Scherer, "The Economics of Parallel Trade in Pharmaceutical Products," (2001), http://www.wto.org/english/tratop_e/trips_e/hosbjor_presentations_e/13scherer_e.doc; "The Pharmaceutical Industry -- Prices and Progress," 929.

[14] See Raymond M. Wolfe, "U.S. Bususinessss R&D Expenditurures Increase in 2006; Companies' Own and Federal Contribubutions Rise," *National Science Foundation, Directorate for Social, Behavioral, and Economic Sciences* (2008), http://www.nsf.gov/statistics/infbrief/nsf08313/nsf08313.pdf.

[15] John-Arne Rottingen et al., "Mapping of Available Health Research and Development Data: What's There, What's Missing, and What Role Is There for a Global Observatory," *Lancet* 382 (2013): 1299, 301.

Figure 3: Gross Domestic Expenditure on Health-Related Research and Development (GERD) as a Percentage of Gross Domestic Product[16]

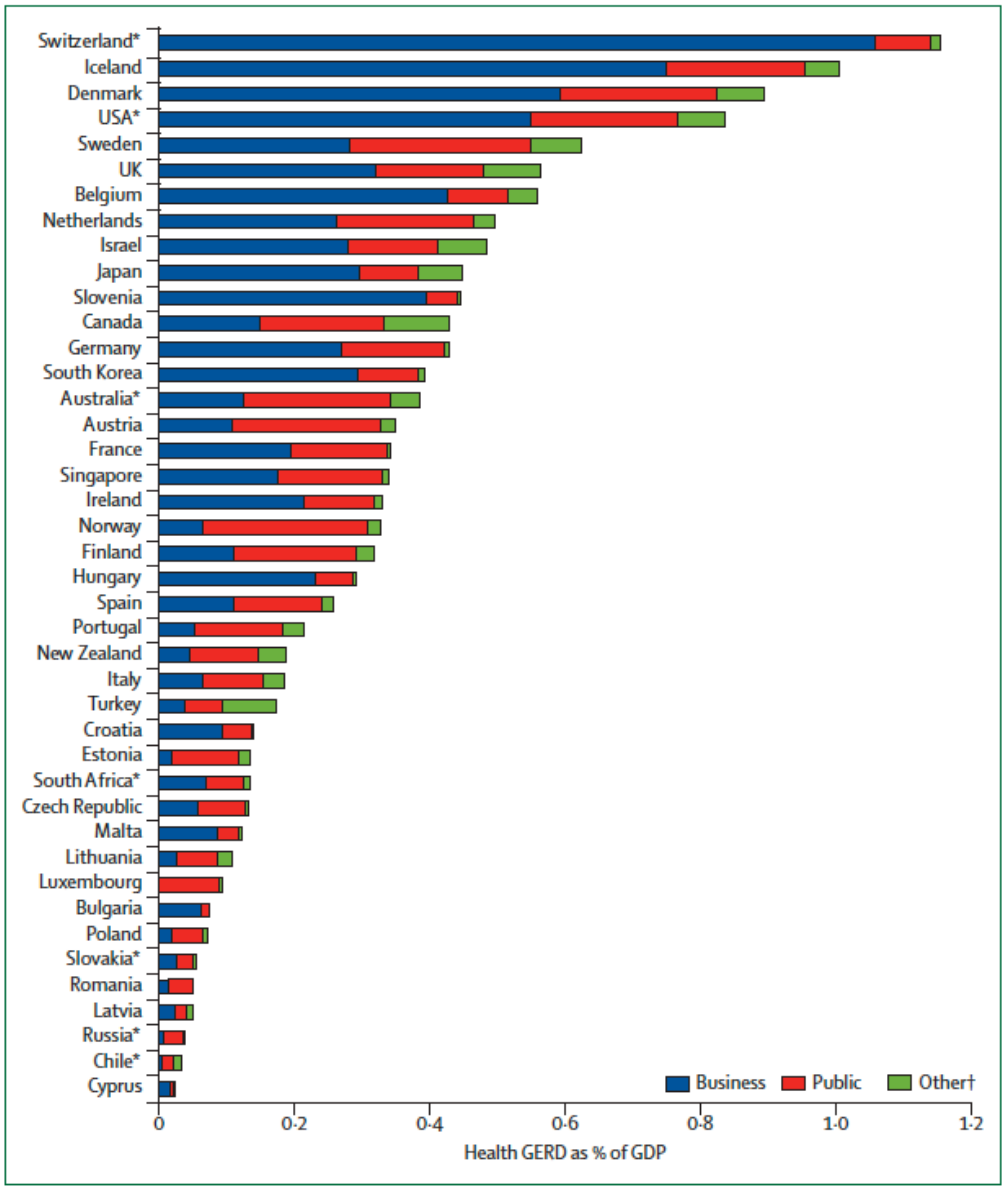

***Figure 3*: Health GERD by estimated broad funding source**

Data are from 2009 unless indicated otherwise. GERD= gross domestic expenditure on research and experimental development. GDP=gross domestic product. *Indicates data from different years: Slovakia 2010; Russia 2009–10; Australia and South Africa 2008–09; Switzerland, USA, and Chile 2008. †"Other" encompasses estimated research and development funds received by government, higher education, and private non-profit institutions from higher education (including the institutional funds of private universities), private non-profit organisations, and from abroad.

All of these numbers are from 2008 or 2009. Since then, investments in health-related R&D in most high-income countries have increased, but not by a great deal. And the relative positions of those countries in terms of spending per GDP have not changed much.

[16] Ibid., 1301.

2. Quality

As Daniel Carpenter has shown, the US government regulates drugs more extensively and aggressively than any other product.[17] The most obvious manifestation of this aggressiveness is the system of "comprehensive licensure": new pharmaceutical products may not be distributed in the United States unless and until they have been approved by the Food and Drug Administration (FDA).

How does the FDA decide which drugs to approve? You might assume that it would do so by weighing the risks and benefits of each candidate. A simple version of this approach would compare (a) the health benefits that could be reaped through distribution and use of the candidate drug with (b) the concomitant potential for harm. To calculate (a), the agency would measure (or demand evidence of) the advantages of the candidate drug over existing drugs and the number of people who would benefit thereby. To calculate (b), the agency would measure (or demand evidence of) the severity of the increased risk of side-effects, injury, or other adverse events posed by distribution and consumption of the candidate. The agency would then approve the drug if and only if (a) exceeded (b). Refinements of these calculations can readily be imagined: use of various discount rates to compare present benefits (and harms) to future benefits (and harms); limitations on the populations who are granted access to the drug (specifically, limitations that could reduce (b) more than (a) and thus improve the ratio of benefits to harms); adjustments to the methods by which both figures are calculated in order to give greater weight to aggregate benefits reaped through generating large improvements in (or threats to) the health of a few people than to aggregate benefits reaped through generating slight improvements in (or threats to) the health of many people;[18] and so forth. But putting such possible refinements aside, the basic approach seems clear enough: drugs should be approved if and only if their distribution would generate net improvements in human health.

Current practice in the US, unfortunately, falls short of such an approach. The primary reason is that the authority of the FDA has been defined, not by a single, comprehensive statute, but by a series of amendments, each provoked by – and thus designed to prevent recurrence of – a particular crisis. The principal provocations and associated legislative responses are summarized in the chart on the following page.[19]

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[17] Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the Fda* (Princeton: Princeton University Press, 2010).

[18] Reasons why we might wish to make such adjustments are considered in Chapter 5.

[19] For much more extensive analyses of this history, see Carpenter, *Reputation and Power*; Krista Hessler Carver, Jeffrey Elikan, and Erika Lietzan, "An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009," *Food and Drug Law Journal* 65 (2010); Anna B. Laakmann, "Collapsing the Distinction between Experimentation and Treatment in the Regulation of New Drugs," *Alabama Law Review* 62 (2011); Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Virginia Law Review* 82 (1996).

Table 1

Crisis	**Response**	**Main Features**
Deaths of children from contaminated smallpox and diphtheria vaccines	Biologics Act of 1902	Biologics may only be manufactured in federally licensed facilities
Rash of dangerous "patent medicines"	1906 Food and Drug Act	Bureau of Chemistry (predecessor of FDA) empowered to initiate punishment of manufacturers of adulterated or misbranded drugs
Narrow interpretation of the 1906 Act in *Johnson* (1911)	1912 Sherley Amendment	"Misbranding" includes making knowingly false statements about therapeutic benefits
Elixir sulfanilimide disaster	1938 Food, Drug and Cosmetic Act	Manufacturers must notify FDA 180 days prior to release; "misbranded" includes "false or misleading in any particular"; duty to disclose adverse evidence
Thalidomide disaster	1962 Kefauver-Harris Amendments	Comprehensive licensure system; agency assesses "effectiveness" as well as safety; FDA interprets "substantial evidence" as requiring two multi-stage randomized controlled trials (RCTs)
Increasingly costly delays in drug approval process	1992 Prescription Drug User Fee Act (PDUFA)	FDA given more resources to accelerate review process
AIDS crisis	1997 Food and Drug Modernization Act (FDAMA)	Codify "fast-track program," including truncated review for promising drugs addressing "life-threatening illnesses"
Increasing uncertainty caused by dual paths for drug approvals	2009 Biologics Price Competition and Innovation Act (BPCIA)	Clarified standards for the evaluation and approval of "biosimilars"

The system generated through this process has important strengths: It's fast; partly because of the PDUFA adjustments, the large majority of applications are now processed in less than 10 months. It does a reasonably good job of preventing unnecessary injuries by keeping dangerous products off the market – a far better job than is achieved through the less

prophylactic regulatory and liability systems that govern most other products. And it at least attempts to deal expeditiously with especially grave illnesses and especially promising responses thereto.

To be sure, even in these respects, the system is not perfect. For example, its speed may have a cost; debate continues concerning whether the fast pace results in a larger number of adverse events.[20] The FDA probably refuses to approve more drugs than it should – because "type 1 errors" (approving unsafe drugs) are so much more visible than "type 2 errors" (disapproving safe drugs).[21] And the agency currently responds less nimbly to urgent health needs or pharmaceutical breakthroughs than the FDAMA sponsors hoped.

But more important (for our purposes, at least) than these imperfections are some fundamental gaps in the process:

- The system measures efficacy by comparing candidates to placebos, rather than to already existing drugs.

- The system fails to compare benefits and harms systematically. Although since 1938, the agency has engaged in some such comparisons under the rubric of assessing "safety," it still does not engage in formal risk-benefit assessment.[22]

- It contains no mechanism for *slowing* the introduction of new drugs when future generations would benefit from less rapid exhaustion of a limited set of potential therapies. (As Kevin Outterson has shown, this defect might have especially unfortunate consequences with respect to antibiotics.[23])

- The agency adheres to the standard sequence of animal trials, followed by three stages of clinical trials, even when that sequence is inappropriate. (For example, as Steven Hyman has shown, animal trial for drugs designed to address neuropsychiatric disorders have never provided useful evidence concerning which of those drugs would prove effective in humans. Thus, use of such trials likely screens out some potentially valuable drugs, but provides us no aid in excluding ineffective drugs.)

- The agency focuses almost all of its energy assessing drugs prior to approval. It rarely withdraws approved drugs from the market and has no systematic way of gathering evidence concerning how drugs, once approved, are performing on ordinary patients.[24]

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[20] See, e.g., Mary K. Olson, "First Drug Launches in the U.S. And Drug Safety," in *Petrie-Flom Drugs Conference* (2009).

[21] Henry Grabowski and John M. Vernon, *The Regulation of Pharmaceuticals: Balancing the Benefits and Risks* (1983), 10.

[22] See Merrill, "The Architecture of Government Regulation of Medical Products," 1764.

[23] See Kevin Outterson, "The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation," *Cardozo Law Review* 31 (2010).

[24] See Laakmann, "Collapsing the Distinction between Experimentation and Treatment in the Regulation of New Drugs."

- The agency tolerates so-called "off label" uses of drugs – but fails to provide physicians or patients useful information concerning safety and efficacy in those contexts.

The defects are not hard to explain. Most are byproducts of the political process through which this regulatory system emerged. It should not be surprising that the system contains features that would prevent recurrence of the particular crises that triggered legislative responses but omits features that would enable a more sensitive and comprehensive assessment of the likely net impact on public health of drug candidates. That explanation, if accurate, is discouraging, because it suggests that comprehensive reform of this system is unlikely in the foreseeable future.

Again, this system finds parallels in other high-income countries. In all, drugs must be approved by at least one government agency before they can be distributed. The criteria used to approve and disapprove drugs sometimes differ modestly from those in the United States. For example, the European Medicines Agency, which since 1995 has had primary responsibility for evaluating drugs in the European Union (and some countries outside the Union), is somewhat slower than the FDA (in part because other government agencies in the participating countries are also involved in marketing approvals) – but also typically somewhat less strict. In addition the way in which the EMA assesses biosimilars and processes post-approval reports from patients are somewhat different. But the large majority of drugs submitted for approval are handled similarly by the two agencies.[25]

3. Access

The third way in which governments seek to manage pharmaceutical products is to increase the likelihood that the people who could benefit from them receive them. Three main strategies for achieving that objective have been identified and tried.

The first is "procurement." Governments sometimes identify drugs from which their residents could benefit, purchase large quantities of those drugs from the private firms that produce them, and then distribute them – at low cost or for free – to consumers, either directly or, more commonly, through intermediaries. The larger the percentage of potential consumers served in this way, the more closely the government approximates a monopsonist – and thus, other things being equal, the lower the price that the government is likely to pay per dose. (Whether that effect should be considered an advantage or a disadvantage depends on factors we will address shortly.)

This system is used infrequently by most developed countries. In the United States, for example, the only major procurement program currently in place is the Vaccines for Children Program, under which the federal government (specifically, the Centers for Disease

[25] For comparisons of the FDA and the EMA, see, e.g., Lynn J. Howie, Bradford R. Hirsh, and Amy Abernathy, "A Comparison of Fda and Ema Drug Approval: Implications for Drug Development and Cost of Care," *Oncology* 27, no. 12 (2013), https://www.cancernetwork.com/oncology-journal/comparison-fda-and-ema-drug-approval-implications-drug-development-and-cost-care.; Slobodan M. Jankovic, "Comparison of Ema and Fda Guidelines for Drug Interactions: An Overview," *Clinical Research and Regulatory Affairs* 31, no. 2-4 (2014).; Anthony J. Hatswell et al., "Regulatory Approval of Pharmaceuticals without a Randomised Controlled Study: Analysis of Ema and Fda Approvals,1999–2014," *BMJ Open* 6 (2016).

Control) purchases directly from private manufacturers vaccines for most common childhood diseases (diphtheria, haemophilus influenza type b, hepatitis A and B, measles, mumps, pertussis, pneumococcal disease, polio, rubella, tetanus, and chickenpox), and then distributes them directly to persons under the age of 18.[26] Roughly half of the childhood population in the United States is currently vaccinated under this program. The success of the program helps to explain the dramatic decrease in the incidence of these diseases in the United States chronicled in the Introduction to this book (although progress along this dimensions is threatened by growing popular resistance to vaccination). Outside of this one setting, however, the US government ordinarily does not procure drugs.

The second of the three strategies is price regulation. By capping the prices that consumers must pay, governments can increase the number of consumers able to purchase the drugs they need. Most developed countries rely heavily on this approach.[27] The United States is an exception. For the most part, the US government lets the market set the price for drugs. Indeed, the government works actively to prevent the price-regulation systems employed in other countries from influencing the market in United States. The primary mechanism it employs for this purpose is an overlapping set of rules that block the importation of drugs into the US, even if they were originally manufactured in this country. Such rules are commonly justified on safety grounds: they are said to shield American consumers against contaminated or counterfeit products. But their principal function is to protect manufacturers against arbitrage – and the resultant downward pressure on the prices they charge in the United States. (In Chapter 4, we will examine in detail the differential pricing practices enabled by these rules.). Some of the legislative proposals currently on the table in the United States would introduce for the first time price regulation of the sort common in continental Europe and Japan, but the prospects for the adoption of such initiatives in the near term are not good.

The last of the strategies is insurance. The ability of consumers to purchase the drugs they need may be enhanced by reimbursing them for some or all of the cost of those purchases. This is the approach upon which the United States currently relies most heavily. In two ways, the US government works to reduce the portion of the prices of drugs that consumers must pay. First and most obviously, it funds programs (Medicaid and Medicare) that wholly or partially cover the costs of prescription drugs for major portions of the American population. Second, it subsidizes private medical insurance by exempting employment-based health-insurance benefits from both payroll taxes and income taxes. As the percentage of total medical costs that consist of the costs of drugs has risen, the percentage of health-insurance plans that cover such costs – and thus the magnitude of the subsidy generated by the tax deductions – has grown.[28] The Patient Protection and Affordable Care Act has increased the scale of these strategies (most importantly, by expanding Medicaid eligibility and by increasing pressure on employers to offer insurance benefits) and added a third type of governmental support for insurance (subsidies given to poor individuals who obtain health insurance through the new insurance exchanges) but has not fundamentally altered the general approach that the United States uses to address the access issue.

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[26] See John E. Calfee and Scott Gottlieb, "Putting Markets to Work in Vaccine Manufacturing," *American Enterprise Institute for Public Policy Research* (2004).

[27] See Patricia Danzon, ed. *Price Comparisons for Pharmaceuticals: A Review of U.S. And Cross-National Studies* (1999); Scherer, "The Pharmaceutical Industry -- Prices and Progress."

[28] See Scherer 929; Weisbrod 1991 523-26; CBO4 47-48; Berndt 2010; Lackawalla.

The government of England currently uses an unusual combination of insurance and indirect price regulation to enhance its citizens' access to pharmaceutical products. The National Health Service reimburses patients for all (or almost all) of the cost of drugs that have received affirmative evaluations from NICE, the National Institute for Health and Clinical Excellence. NICE, in turn, takes into account the price of drugs when deciding whether they are sufficiently cost effective to warrant recommendation. The net effect is to put pressure on pharmaceutical firms to lower the prices of drugs, lest they not receive NICE's imprimatur. The high cost to the government of this system may contribute to the slow pace at which NICE makes its evaluations, but drugs that do receive one of its positive assessments are readily available everyone who needs them.[29]

4. Gaps and Conflicts

As we have seen, the three dimensions of governmental management of pharmaceutical products are handled through different statutory mechanisms administered by different government agencies. Occasionally in the United States, Congress pays attention to more than one dimension simultaneously and attempts to make the pieces fit together. The clearest example is the Hatch-Waxman Act, which was mentioned above. For the most part, however, the three zones are autonomous. No governmental institution has the power or incentive to coordinate them.

The lack of coordination has unfortunate effects. To be sure, every now and then, an initiative in one sector will generate fortuitous benefits in another sector. For instance, the new rules governing follow-on biologics (designed for safety) may have the incidental effect of increasing the costs borne by generic firms, which in turn will raise barriers to entry into markets for pioneering drugs whose patents have expired, which in turn will increase incentives for innovation in biologics.[30] Much more often, however, the failure of the designers or managers of one sector to take into account impacts on the other sectors lead to one of two problems: Either their initiatives needlessly exacerbate the problems that the other sectors are trying to solve, or no one takes responsibility for a particular issue, and it falls through the cracks.

The most serious manifestation of the first type of problem involves cost. Our reliance upon the patent regime and data-exclusivity rules to stimulate innovation causes (indeed, depends upon) an increase in the price of drugs, which in turn increases the difficulty of ensuring that the people who need those drugs have access to them. In other words, the way we approach the incentive problem exacerbates the access problem. A less obvious contributing factor: our continued reliance upon the "gold standard" of clinical testing to ensure the safety and efficacy of drugs (even in settings where that approach has proven less than optimal) increases the cost of securing approval for new drugs, which in turn necessitates extensions of the term of patent protection (to enable the firms to recoup those costs), which

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[29] See Joshua Cohen et al., "Comparing Patient Access to Pharmaceuticals in the Uk and Us," *Appl Health Econ Health Policy* 5, no. 3 (2006).

[30] Cf. Henry Grabowski, Ian Cockburn, & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve*?, 25 Health Aff. 1291 (2006).

in turn further worsens the "access" problem.[31] Last but not least, our heavy reliance upon insurance (rather than price controls or procurement) to overcome the access problem raises costs still further, by reducing the incentives for consumers or physicians to engage in cost/benefit analyses when selecting medicines, which in turn reduces the reasons for manufacturers to set limits on prices.[32] This last dynamic is curbed to some extent by the cost sensitivity of the public and private insurers, which in turn prompts manufacturers to pay the insurers secret rebates in order to retain privileged positions in their formularies. However, pressure from physicians and consumers and incomplete coordination among the insurers when making formulary decisions limit the effectiveness of this check.[33] The net results: drug prices in the United States are among the highest in the world; the US market for drugs is by far the largest in the world (currently accounting for roughly 40% of the global market[34]); and the research efforts of pharmaceutical firms focus disproportionately on diseases common in the United States.

The dynamic is no secret. In various ways, the insurers are trying to mitigate it – for instance, by demanding the right to participate in the choice of medicines and by adjusting co-payments to try to nudge consumers toward generic alternatives to branded drugs.[35] But these remedies are at best palliative. To cure this problem, we would have to alter fundamentally the way in which we deal with at least one of the three dimensions.

The second example of this type of problem is less well known but equally serious: We currently rely too heavily on medicines, which cure (or relieve the symptoms of) diseases after they have been contracted, and too little on vaccines, which prevent diseases in the first instance. The data are chilling. Only 54 vaccines are currently licensed for use in the United States,[36] and the major pharmaceutical firms are investing discouragingly little money in research designed to develop new ones. As a result, the percentage of drugs approved each year by the FDA that consist of vaccines has been dropping in recent years. From a high of 14% in 2006-2008, it has now fallen to 5%.[37]

In a classic essay, Burton Weisbrod offered the following illustration of the relative merits of vaccines and cures. In the early 20th century, he pointed out, we lacked any effective treatment for polio. The result was that the total health care costs associated with polio were low. "Many victims of the disease died quickly as a result of paralysis; for them, the effects were disastrous, but the attendant health care costs were small." The development and

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[31] See Eisenberg, "The Role of the Fda in Innovation Policy."36; David A. Kessler, Rose, Janet L, Temple, Robert J., Schapiro, Renie and Griffin, Joseph P., "Therapeutic Class Wars -- Drug Promotion in a Competitve Marketplace," *New England Journal of Medicine* 331, no. 2 (1994).

[32] Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," 4-5.

[33] See Joshua Cohen et al., "Comparing Patent Access."

[34] See Berndt and Newhouse, "Pricing and Reimbursement in U.S. Pharmaceutical Markets."

[35] See Darius Lakdawalla, "Insurer Bargaining and Negotiated Drug Prices in Medicare Part D*," in *Petrie-Flom Drugs Conference* (2009).

[36] FDA, "Vaccines Licensed for Use in the United States," https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states (current as of 11/27/2019) (counting as one identical vaccines manufactured by more than one company).

[37] See Jonathan J. Darrow, Michael S. Sinha, and Aaron S. Kesselheim, "When Markets Fail: Patents and Infectious Disease Products," *Food and Drug Law Journal* 73 (2018): 364.

deployment of iron-lung technology "prolonged life, but at substantial cost." Those costs remained high, until the development of polio vaccines (Sabin and Salk), whose widespread distribution (in the United States) virtually eliminated the disease. (There were 38,000 cases in 1954; 5 cases in 1985.) The result is that we now devote virtually no resources to combatting polio.[38] The lesson is plain: vaccines have enormous potential both to alleviate suffering and to reduce costs.

Why, then, are we neglecting vaccines? Explanations differ. Some of the factors are not directly relevant to our inquiry here. For instance, the methods by which vaccines have traditionally been produced are more expensive than the methods used to produce most medicines – and thus the potential profits they can generate are smaller. In addition, some analysts think that, even after a modest adjustment of the relevant products-liability regime, the large potential damages to which vaccine producers are potentially exposed discourages entry.[39] And so forth.

But some of the contributing causes do implicate the three dimensions of governmental management that we have outlined. For example, high-profile scandals involving impure vaccines have resulted in the imposition on vaccine producers of unusually tight and costly safety regulations. Even more problematic may be the understandable efforts of the administrators of the vaccine procurement programs to use their bargaining power to drive down costs. Their success in that regard helps the current generation, by getting existing vaccines into their mouths cheaply, but may hurt the next generation, by reducing incentives to hunt for new vaccines. In short, our efforts to promote safety (sector 2) and to increase access (sector 3) have had the unfortunate effect of exacerbating the inadequate incentives to innovate in this area (sector 1).

Nor can the government respond to this problem by dialing up incentives – because we have no dials to turn. As we have seen, in order to stimulate and guide applied research, we rely in the United States almost exclusively upon market signals. Unusual characteristics of the market for vaccines (such as the inability of sellers to monetize the positive externalities associated with vaccine consumption and the tendency of potential consumers to underestimate the risks of contacting the diseases to which they pertain) make those signals especially unreliable.[40]

In sum, our current regime is analogous to a situation in which a patient has three doctors, each concerned with a different ailment. Each physician prescribes a medicine designed to alleviate the condition with which he is concerned, but without considering the impact on the other two conditions or on the efficacy of the medicines prescribed by the other two doctors. The result is rarely beneficial and sometimes catastrophic.

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[38] Burton Weisbrod, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment," *Journal of Economic Literature* 29, no. 2 (1991).

[39] See Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* (2004).

[40] See Michael Kremer and Rachel Glennerster, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* (Princeton, N.J.: Princeton University Press, 2004), , 29ff.

Adverse interaction of these sorts is not the only drawback of our current regime. Equally important is inattention to some crucial issues. Questions that fall into no one's portfolio are ignored – sometimes at great social cost. The two most fundamental gaps are summarized below.

The pharmaceutical industry currently devotes too many resources to generating so-called "me-too" drugs and modest improvements on existing drugs and devotes too few resources to pursuing genuine breakthroughs. Among the indicators of the problem: 78% of all drugs (and 59% of NMEs) licensed in the United States between 1990 and 2004 consisted of "me-toos."[41] This problem could be alleviated through adjustments in any of the three sectors of governmental control. For example, the patent system could be modified (or construed) to alter the nonobviousness ("inventive step") standard to make it harder to secure protection for minor advances – or by increasing the rewards (perhaps through extended terms of protection) for major advances. The Supreme Court of India recently took a step in that direction,[42] but the courts in the United States have not. Alternatively, the FDA could be empowered to undertake genuine cost/benefit analyses of candidate drugs and then favor highly beneficial innovations or disfavor minor variations. A third possibility: government-run or subsidized insurance systems could be adjusted to deny reimbursement for me-too drugs. In other words, any of the three physicians could address this problem, but none does. The net result: the bias continues.

The second example is simpler – and, for our purposes, even more important. The current combination of incentives and regulatory regimes directs resources toward research projects that promise to generate drugs for which there are large and lucrative markets, at the expense of projects that would have larger net health benefits but would generate fewer profits.[43] A market, to be lucrative market, must include a large number of persons suffering from a particular ailment who have both the ability and the willingness to pay substantial sums for protection or relief. The large (and in most cases growing) sets of people suffering from noncommunicable diseases in high-income countries (and above all, the United States) means that lucrative markets for drugs that address all of those ailments exist. By contrast, the markets for the equally deadly infectious diseases now concentrated in developing countries are much smaller.

The impact on the patterns of health-related research and development has been dramatic. The shares of total investment and of clinical trials devoted to infectious diseases have long been well below the shares that would match the global disease burdens associated with those diseases.[44] Investment in the neglected tropical diseases have been especially low

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[41] [Update with more refined numbers from Joseph A. DiMasi and Cherie Paquette, "The Economics of Follow-on Drug Research and Innovation: Trends in Entry Rates and the Timing of Development," *Pharmacoeconomics* 22 (2004). On excessive investment in IMPs, see Mark Duggan and Fiona Scott Morton, "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing," *Quarterly Journal of Economics* 71, no. 1 (2006).]

[42] Cf. Novartis AG v. Union of India, Civil Appeal Nos. 2706-2716 (Supreme Court of India 2013), available at http://www.scribd.com/doc/133343411/Novartis-patent-Judgement.

[43] Among the many sources exploring this problem are Kremer and Glennerster, *Strong Medicine*; Michael R. and Dranove Ward, David, "The Vertical Chain of Research and Development in the Pharmaceutical Industry," *Economic Inquiry* 33, no. 1 (1995).

[44] See Darrow, Sinha, and Kesselheim, "When Markets Fail."

– less than 1% of the global total.[45] These biases are confirmed by other indicators: Of clinical trials, 89% focus on Type I diseases, 9.1% focus on Type II diseases, and 1.9% focus on Type III diseases.[46] And at the end of the research chain, the percentages of drug approvals that involve anti-microbial drugs are low – and have been declining since the 1980s.[47]

In short, the most important side-effect of the way in which high-income countries manage pharmaceutical products has been underfunding research on vaccines and on drugs aimed at the set of diseases that disproportionately afflict the residents of poor countries.

B. Developing-Country Governments

As sources of both causes and potential solutions to the global health crisis, the systems used by the governments of developing countries to manage pharmaceutical products are as important as the systems used by developed countries. It would be infeasible to catalogue all of the systems found in the developing world. In this section, we examine those of five countries that, collectively, are reasonably representative: Malawi, Namibia, Cambodia, Thailand, and the Plurinational State of Bolivia (hereinafter "Bolivia").

The following factors contributed to the selection of these five: Two are located in subSaharan Africa, the region where, as we have seen, the greatest burdens from infectious diseases are currently found; two are located in Southeast Asia, the next-most afflicted region, and one is in South America, the third in line. None of the five is currently involved in warfare or violent civil strife, which would distort our analysis of their health-care institutions or complicate our efforts to suggest reforms. Finally, we are already providing advice to the governments of two of the countries – Malawi and Namibia – and thus happen to know a fair amount about them.

1. Background

The following table presents some basic information about these five countries – and compares them to the United States.

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[45] See Rottingen et al., "Mapping R&D Data," 1303.

[46] See ibid. This categorization was discussed in the Introduction. For itemization of the diseases that fall into each category, see WHO Secretariat, "Defining Disease Types I, II, and III (2012), https://www.who.int/phi/3-background_cewg_agenda_item5_disease_types_final.pdf.

[47] Darrow, Sinha, and Kesselheim, "When Markets Fail."

Table 2

	Malawi	Cambodia	Bolivia	Namibia	Thailand	USA
Population (2018)[48]	18,143,310	16,249,800	11,353,140	2,448,260	69,428,520	327,167,430
Gross National Income per capita (nominal) (2018)[49]	$360	$1,380	$3,370	$5,250	$6,610	$62,850
Gross National Income per capita (PPP) (2018)[50]	$1,310	$4,060	$7,670	$10,920	$18,200	$63,390
GINI coefficient (2019)[51]	46.1	37.9	47	59.7	44.5	45
IHDI (2018)[52]	0.346	0.465	0.533	0.418	0.635	0.797
Healthy Life Expectancy (2016)[53]	56.2	60.8	63.0	55.9	66.8	68.5
Infectious Disease Burden (2016)[54]	16,300	4,000	2,867	14,900	2,462	500
Infectious Disease Mortality (2016)[55]	250	66	41	250	52	17
Healthcare expenditure (% of GDP)[56]	9.83%	6.08%	6.86%	9.12%	3.71%	17.07%
Physicians per 100,000 population[57]	1.57	16.82	161.11	37.21	80.96	259.48

Malawi is a small, landlocked country in eastern Africa. It is currently one of the poorest countries in the world; its GNI per capita (whether measured in raw dollars or using the purchase-power-parity method) places it close to the bottom of the list of countries. In

[48] Source: World Bank, "Population by Country," https://data.worldbank.org/indicator/SP.POP.TOTL.

[49] Source: World Bank, "GNI per capita, Atlas Method (current US$)," https://data.worldbank.org/indicator/ny.gnp.pcap.cd?year_high_desc=true.

[50] Source: World Bank, "GNI per capita, PPP (current international $)," https://data.worldbank.org/indicator/NY.GNP.PCAP.PP.CD?year_high_desc=true.

[51] The GINI coefficient is the most commonly used measure of income inequality. All data are drawn from: World Population Review, "Gini Coefficient by Country, 2019," http://worldpopulationreview.com/countries/gini-coefficient-by-country/.

[52] The Inequality Human Development Index (IDHI) combines several measures of economic and social development – and then adjusts the combination downward to take into account the impact of economic inequality. These data are derived from United Nations Development Programme, Inequality Human Development Index (IDHI), Country Profiles," http://hdr.undp.org/en/countries/profiles/MWI; http://hdr.undp.org/en/countries/profiles/KHM; http://hdr.undp.org/en/countries/profiles/HTI; http://hdr.undp.org/en/countries/profiles/NAM; http://hdr.undp.org/en/countries/profiles/USA.

[53] Source: World Health Organization, "Healthy Life Expectancy: Data by Country," https://apps.who.int/gho/data/node.main.HALE?lang=en.

[54] Measured in DALYs per year per 100,000 population. All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

[55] Measure in deaths per year per 100,000 population. All data are from Ibid.

[56] Source: World Bank, "Current Health Expenditure (% of GDP)," https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS. Although this database is current as of 2019, the numbers for all five countries come from 2016.

[57] Source: World Health Organization, "Medical Doctors," http://apps.who.int/gho/data/node.main.HWFGRP_0020?lang=en. Unfortunately, these numbers come from different years and thus provide only a rough indication of the relative numbers of medical doctors in the five countries. The number for Malawi is not a misprint.

terms of inequality of income, however, it is roughly comparable to the United States – and less unequal than some of its neighbors, such as South Africa and Botswana.

19% of the roughly 18 million residents of Malawi live in cities; 81% live in the countryside. Agricultural occupations predominate. Until recently, tobacco was the main crop, but declining prices and international boycotts of Malawi tobacco (relating to reports of child labor) are prompting many farmers to shift to soybeans, tea, and sugar.[58]

Malawi has a relatively stable democratic system of government. Currently, the dominant party is the Democratic Progressive Party, led by President Peter Mutharika.

Life expectancy in Malawi is much lower than in the United States – or in other developed countries. The main cause of the discrepancy is the prevalence of infectious diseases. The diseases that weigh most heavily (measured by DALYs per 100,000 residents) are HIV (8,521), malaria (2,747), diarrhoeal diseases (2,297), meningitis (626), and tuberculosis (623).[59]

Malawi's health-care system has four sectors: a public sector funded and run by the government; a for-profit private sector; a non-profit private sector (mission hospitals and the Christian Health Association of Malawi [CHAM]); and an "informal" sector (traditional healers, herbalists, and prophets).[60]

Usage of the informal sector, particularly in rural areas, is high. For example, one study found that, of persons with chronic noncommunicable diseases, 37.3% did not seek any medical care, 42.5% sought formal care, and 20.2% relied on informal care).[61]

Among the formal sectors, the public sector is by far the largest. The relatively high ratio of total healthcare expenditure to the country's GDP (9.83%) is made possible by large subsidies to the public sector by international donors.

Medical services and medicines in the public sector are free; institutions in the private sectors charge modest fees. The availability and quality of the services in the private sectors are widely thought to be better than the public sector. All sectors are desperately short of trained medical doctors, but the shortage is greatest in the public sector.

The systems for distributing drugs in Malawi are imperfect. Poor storage conditions cause some medicines to degrade, and imperfections in the supply chain frequently result in stock-outs in hospitals and pharmacies.[62]

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[58] See The Economist, "Country Report: Malawi," September 26, 2019.

[59] All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

[60] See Ariane McCabe et al., "Private Sector Pharmaceutical Supply and Distribution Channels in Africa: A Focus on Ghana, Malawi and Mali," in *HNP Discussion Paper* (World Bank, 2011), 12.; Emily Fisher, Rebecca Lazarus, and Ramin Asgary, "Attitudes and Perceptions Towards Access and Use of the Formal Healthcare Sector in Northern Malawi," *Journal of Health Care for the Poor and Underserved* 28, no. 3 (2917).

[61] See Qun Wang et al., "Health Seeking Behaviour and the Related Household out-of-Pocket Expenditure for Chronic Non-Communicable Diseases in Rural Malawi," *Health Policy and Planning* 30 (2015).

[62] See McCabe et al., "Pharmaceutical Supply in Africa," 25-26.

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Namibia is located roughly a thousand miles to the southwest of Malawi. Its land area is much larger, but its population is smaller: roughly 2.7 million residents. The paucity of people is related to its climate; Namibia is extremely dry and becoming more so. Two thirds of its population live in rural areas.

Namibia is nowhere near as impoverished as Malawi. The GNI per capita of $5,250 places it slightly above the boundary (set by the World Bank) between lower-middle-income and upper-middle-income countries. Severe income inequality, however, means that most residents remain very poor.

In other respects, Namibia resembles Malawi. It has a stable democratic system of government. Healthy life expectancy in the two countries is nearly identical. Infectious diseases are common, although the set of diseases that are most problematic is somewhat different. (The most burdensome in Namibia (measured by DALYs per 100,000 residents) are HIV (10,391), diarrhoeal diseases (1681), tuberculosis (1383), meningitis (362), and malaria (326).)[63]

As in Malawi, health care in Namibia is delivered through four main sectors: a large public sector, used most heavily by the poor, a much smaller for-profit private sector, a modest nonprofit private sector, and an informal sector. Medicines distributed by public-sector pharmacies and hospitals are free, but the quality of services in the public sector is generally considered low, primarily because of the shortage of qualified staff. Private health insurance (typically used to cover services and medicines in the private sector), is available, but less than 20% of the population is able to afford it.[64]

Almost all medicines are imported. Typically, they arrive at the Central Medical Stores in Windhoek, where they are kept until they are distributed to hospitals and pharmacies. Neither the Central Medical Stores nor most hospitals have facilities for controlling storage temperatures.

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Cambodia is as damp as Namibia is dry. For most of the twentieth century, the country suffered from waves of colonization, war, and genocide, but is now relatively peaceful. Formally, its government combines an elective constitutional monarchy with a multiparty democracy, but in practice it is authoritarian, dominated by the Cambodian People's Party and Hun Sen, the longtime Prime Minister.

Cambodia's GNI per capita is low enough that it, like Malawi, has been designated by the United Nations a "least developed country." However, a high economic growth rate and

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[63] All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

[64] The insurance is provided by ten "medical aid funds," run by for-profit administrators. Six are limited to the employees of particular firms or institutions, but four are open to members of the public. See Benedikt Brockmeyer, "The Health System in Namibia: Deliberations About an Affrodable National Health Insurance for the Low-Income Workforce in Namibia," (2012), 2-5.

modest levels of income inequality have enabled the country in recent years to reduce significantly the poverty rate. The major industries are agriculture, textiles, and tourism.

The most burdensome infectious diseases in Cambodia (measured by DALYs per 100,000 residents) are tuberculosis (812), diarrhoeal diseases (739); HIV (638); Meningitis (192); and Hepatitis B (147).[65] The burden associated with malaria is modest (only 6 DALYs per 100,000 residents), but the high percentage of drug-resistant strains in the western part of the country poses a severe long-term threat, not just to the population of Cambodia, but also to the rest of the world.[66]

Decimated during the Khmer Rouge period, the healthcare system in Cambodia has gradually been rebuilt, partly with major donations from international organizations. The net result has been a sharp improvement in life expectancy.[67]

The overall structure of the healthcare system in Cambodia parallels those of Malawi and Namibia, but the private sector is proportionally much larger, and the public sector much smaller than in either of those countries. One consequence is that (as of 2014) 62% of total health expenditures consisted of out-of-pocket payments by patients – an extremely high number.[68] Some employers offer health insurance, but the percentage of the population that is covered by it is small.[69] The government, aided by the World Health Organization, seems determined to increase the quality and accessibility of health care by establishing a broad social-security system, but progress toward that goal has been slow.[70]

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Thailand, located immediately to the west of Cambodia, is more prosperous and populous. Its nominal GNI per capita of $6,610 is slightly above that of Namibia, placing it

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[65] All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

[66] See Arjen M. Dondorp et al., "Artemisinin Resistance in Plasmodium Falciparum Malaria," *New England Journal of Medicine* 361 (2009).; Richard J Maude et al., "The Last Man Standing Is the Most Resistant: Eliminating Artemisinin-Resistant Malaria in Cambodia," *Malaria Journal* 8, no. 31 (2009).(" The model predicts that if there is no intervention, and use of artemisinin monotherapies continues, there will be an exponential rise in the proportion of resistant infections and a slowly increasing prevalence of infection. By 2030, the model predicts that the prevalence of malaria will have doubled compared to 2008 and resistance to the artemisinins will be approaching 100%.")

[67] See WHO, "Cambodia-Who Country Cooperation Strategy 2016-2020," (2016), 2.; Khim Keovathanak and Peter Leslie Annear, "The Transition to Semi-Autonomous Management of District Health Services in Cambodia: Assessing Purchasing Arrangements, Transaction Costs, and Operational Efficiencies of Special Operating Agencies," in *Improving Health Sector Performance: Institutions, Motivations and Incentives*, ed. Hossein Jalilian and Vicheth Sen (2011).

[68] See WHO, "Cambodia-Who Country Cooperation Strategy 2016-2020," 5-6. Cf. Wim Van Damme et al., "Out-of-Pocket Health Expenditure and Debt in Poor Households: Evidence from Cambodia," *Tropical Medicine and International Health* 9, no. 2 (2004).(showing that the percentage was even higher a decade earlier).

[69] See Sopheap Ly, "Social Health Insurance in Cambodia: An Analysis of the Health Care Delivery Mechanism," in *Improving Health Sector Performance: Institutions, Motivations and Incentives*, ed. Hossein Jalilian and Vicheth Sen (2011).

[70] See WHO, "Cambodia-Who Country Cooperation Strategy 2016-2020."; Ly, "Social Health Insurance in Cambodia: An Analysis of the Health Care Delivery Mechanism."

too in the category of upper-middle-income countries. Despite a series of political convulsions in the late 20th century and early 21st centuries, the Thai economy has grown at an impressive pace, powered by a combination of manufacturing, large-scale agriculture, and tourism.[71] Adult literacy is high, and unemployment is low.

Two unrelated characteristics make Thailand's healthcare system unusual. First, it has a thriving business in what is loosely called "medical tourism." Residents of other countries (most of them from the middle class) frequently travel to Thailand to receive surgical or other services, which are both high-quality and (for them) affordable. (Some combine such trips with vacations in Thailand; hence the odd label for this practice.) For wealthy residents of Thailand, medical tourism has had the incidental benefit of increasing the sophistication of the facilities and physicians available locally – although at the cost of reducing the ability of the Thai middle class to afford those services.[72]

Second, since 2002, Thailand has had a system of universal health care. Today, residents not covered by insurance and unable to afford private health care can obtain, for free, care in regional public hospitals (most of them publicly funded) and, if necessary, secondary and tertiary-care facilities. 75% of the Thai population uses the system. Low funding rates and a shortage of doctors (partly caused by a "brain drain" from the public to the private sector fueled by medical tourism) limit the quality of care in the system, but it is still substantially better than that available to poor residents of most similarly situated countries.[73]

Despite these advantages, Thailand still has a serious problem with infectious diseases. Indeed, its HIV burden (1,205 DALYs per 100,000 residents) is double that of Cambodia. The next most burdensome diseases are tuberculosis (299), diarrhoeal diseases (274); and meningitis (96).[74]

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[71] See https://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG?locations=TH. The only major exception was during the Asian economic crisis between 1996 and 1999, from which the country recovered quickly, in part because of robust exports.

[72] See Erik Cohen, "Medical Tourism in Thailand," *AU-GSB e-Journal* 1, no. 1 (2008); Nicola S. Pocock and Kai Hong Phua, "Medical Tourism and Policy Implications for Health Systems: A Conceptual Framework from a Comparative Study of Thailand, Singapore and Malaysia," *Globalization and Health* 7, no. 12 (2011).

[73] See Seung Chun Paek, Natthani Meemon, and Thomas T.H. Wan, "Thailand's Universal Coverage Scheme and Its Impact on Health-Seeking Behavior," *SpringerPlus* 5 (2016); Viroj Tangcharoensathien et al., "Monitoring and Evaluating Progress Towards Universal Health Coverage in Thailand," *PLOS Medicine* 11, no. 9 (2014); Vasoontara Yiengprugsawan, Matthew Kelly, and and Adrian C. Sleigh1 Sam-ang Seubsman2, "The First 10 Years of the Universal Coverage Scheme in Thailand: Review of Its Impact on Health Inequalities and Lessons Learnt for Middle-Income Countries," *Australas epidemiol.* 17, no. 3 (2010); Viroj Tangcharoensathien et al., "Promoting Universal Financial Protection: How the Thai Universal Coverage Scheme Was Designed to Ensure Equity," *Health Research Policy and Systems* 11, no. 25 (2013); Supon Limwattananon et al., "Why Has the Universal Coverage Scheme in Thailand Achieved a Pro-Poor Public Subsidy for Health Care?," *BMC Public Health* 12 (2012).

[74] All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

Bolivia is the second most impoverished country in the western hemisphere, trailing only Haiti. It has long been highly stratified. Wealth and political power has been concentrated in the hands of the descendants of the Spanish colonizers. Members of the many indigenous groups, most living in the countryside, have been far worse off.

Until recently, the Bolivian health-care system was similarly stratified. The rich received decent care in the private sector, while the poor received low-quality care in the underfunded and understaffed public sector or relied on traditional medicines and services.[75] Partly as a result, life expectancy in the country was low – 56.0 in 2000, and 58.5 in 2005.[76]

In 2006, Evo Morales became the first Bolivian president of indigenous descent. Reforms designed to improve the lives of the rural poor followed quickly. With respect to health care, Morales instituted a system of incentives designed to reduce infant and maternal mortality, created several programs for augmenting the nutrition available to the poor, and cooperated with Cuba to increase the number of physicians in Bolivia.[77] Finally, just before his ouster as President in 2019, Morales announced the establishment of the Sistema Único de Salud ("SUS"), which would provide universal health care.[78]

The impact of these reforms has been substantial – but not as radical as was hoped.[79] Life expectancy in Bolivia is still lower than in any other South American country. Most relevant for our purposes is the continued incidence of infectious diseases. The most burdensome (measured by DALYs per 100,000 residents) are diarrhoeal diseases (806), HIV (414), Tuberculosis (386), Syphilis (167), Meningitis (130), and Chagas (130).[80]

In short, Bolivia has made great strides in the field of public health in general, and the fight against infectious diseases in particular. But whether Morales' successors will be both willing and able to implement his vision of universal, high-quality health care remains to be seen.

We now turn to how each of these nations have sought to address the three dimensions of pharmaceutical management.

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[75] See, e.g., Ina Vandebroek et al., "Comparison of Health Conditions Treated with Traditional and Biomedical Health Care in a Quechua Community in Rural Bolivia," *Journal of Ethnobiology and Ethnomedicine* 4, no. 1 (2008).; Henriette Bruun and Beth Elverdam, "Los Naturistas—Healers Who Integrate Traditional and Biomedical Explanations in Their Treatment in the Bolivian Health Care System," *Anthropology & Medicine* 13, no. 3 (2006).

[76] Source: https://apps.who.int/gho/data/node.main.HALE?lang=en.

[77] See Tim B Heaton et al., "Inequalities in Child Health in Bolivia: Has Morales Made a Difference?," *Health Sociology Review* 23, no. 3 (2014).

[78] See Morning Star, "Bolivia Introduces Health Care for All," *People's World*, March 4, 2019 2019.; Ernesto Londono, "Bolivian Leader Evo Morales Steps Down," *New York Times*, November 13, 2019 2019.

[79] See Tim B Heaton et al., "Inequalities in Child Health in Bolivia: Has Morales Made a Difference?."

[80] All data are from World Health Organization, "Disease Burden and Mortality Estimates: WHO Member States, 2016," https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

2. Incentives

As we saw, the United States currently uses a combination of government grants and intellectual-property law to provide incentives for the development of new pharmaceutical products (although only a modest amount of the roughly $115 billion per year in total R&D expenditures generated by those systems is applied to projects involving the infectious diseases that afflict developing countries). On a per capita basis, the expenditures by most other developed countries are similar.

Of the five developing countries we are considering, only Thailand employs the first of these strategies to any significant degree. Very recently, the government has begun to begun to use a combination of grants and tax breaks to fuel research in biotechnology.[81] To date, public investment in pharmaceutical research in the other four countries has been negligible.[82]

With respect to the second device – intellectual property law – the situation is more complicated and unstable. All five countries are members of the World Trade Organization and, as a result, are obliged to establish national patent systems that, very roughly speaking, resemble the system in place in the United States. However, the degree to which they thus far approximated the US model varies sharply.

Malawi and Cambodia are both classified by the United Nations as "least developed countries"[83] and thus are not required by the relevant treaties to extend patent protection to pharmaceutical products until at least 2033.[84] They are free to do so, but neither has.

The other three countries are not considered "least developed" and thus must recognize pharmaceutical patents. In 2012, Namibia adopted a new patent statute, which (among other things) complied with this obligation. However, regulations essential to the implementation of the new statute have not yet been adopted. Reportedly, no patent on a pharmaceutical product is currently in force in Namibia.[85]

Bolivia is a member of the Andean Community of Nations and thus adheres to Decision 486, which (among other things) governs the requirements for patent protection. Pharmaceutical products are deemed patentable under Decision 486. However, Article 20(b) of the Decision excludes from patent protection "inventions, when the prevention of the commercial exploitation within the respective Member Country of the commercial exploitation is necessary to protect human or animal life or health."[86] In 2007, President

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[81] See "Interview: Nares Damrongchai – Ceo, Thailand Center of Excellence for Life Sciences (Tcels)," *Pharma Boardroom*, Augustt 24, 2015; Jean-François Tremblay, "Thailand Embarks on Life Sciences Push: Reversing Its Long Neglect of R&D, Southeast Asian Country Now Encourages Biotechnology Innovation," *Chemical & Engineering News* 95, no. 21 (2017); Anna Rose Welch, "What to Know About Thailand's Life Sciences Industry," *Biosimilar Development*, May 12, 2017 2017.

[82] See Rottingen et al., "Mapping R&D Data."

[83] See https://www.wto.org/english/thewto_e/whatis_e/tif_e/org7_e.htm.

[84] See "WTO Drugs Patent Waiver for LDCs Extended until 2033," https://www.un.org/ldcportal/wto-drugs-patent-waiver-for-ldcs-extended-until-2033/.

[85] [verify with BIPA].

[86] Andean Community, Decision 486, Common Intellectual Property Decree, http://www.sice.oas.org/Trade/Junac/Decisiones/DEC486ae.asp#tit2c1.

Morales announced Supreme Decree 29004, which implemented that exclusion (and various other provisions of Bolivian law) by creating a "special procedure for the treatment of pharmaceutical products." The Unit of Medicines and Health Technology, a governmental body separate from the Intellectual Property Service, was required to review all patents on such products to determine whether "the content and scope for which protection is sought … interfere with the right to health and access to medicine." A positive determination would result in rejection of the patent.[87] Since the adoption of this system, it appears that no pharmaceutical product patents have been issued in Bolivia.[88]

Of the five countries, the only one in which patent protection for pharmaceutical products is regularly invoked is Thailand. In 1992, strong pressure from the United States prompted Thailand to recognize patent protection for drugs.[89] Pharmaceutical firms quickly began to apply for and receive patents on new products.[90] However, in the judgment of the firms, Thailand's law was insufficiently protective. Starting in 2003?, as part of the prolonged negotiation of a Free Trade Agreement between the two countries, the United States Trade Representative, responding to the firms' concerns, pressed Thailand to adopt additional shields, such as extensions of the patent terms to offset delays in the processing of applications, recognition of the patentability of biological processes and genes, and data exclusivity protections.[91] The initiative might well have succeeded were it not for a 2006 coup in Thailand, which forced a halt to the negotiations. The net result is that the reforms sought by the firms and the USTR were never adopted and the Thai patent regime remains, in their eyes, imperfect.

Among its imperfections is the amount of time it takes the Thai patent office (the Department of Intellectual Property or "DIP") to process applications. Reportedly, the average delay between the date of the application for a patent on a drug and the date on which it issues is 12 years. That is substantially longer than the typical duration in the United States, Europe, or Japan.[92] This may simply be due to insufficient staffing. Alternatively, it may reflect the time required to implement an unusual step in the Thai process for examining applications: the solicitation of public comments with respect to whether the technology in question satisfies the "inventive step" requirement.

Other aspects of the system, however, mitigate its slow pace. Reportedly, firms with pending patent applications have been able to discourage generic firms from entering into competition with them by threatening to litigate as soon as the patents issue. And the DIP

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[87] Official Gazette of Bolivia, Supreme Decree No. 29004 (English translation by WIPO); Silvia Roxana Frias Villegas, Report SNP/2014/02118 (May 7, 2014), 2-3.

[88] [Recheck with Ramiro Moreno Baldivieso.]

[89] See Jakkrit Kuanpoth, "Compulsory Licences: Law and Practice in Thailand," in *Compulsory Licensing: Practical Experiences and Ways Forward*, ed. Reto M. Hilty and Kung-Chung Liu (Berlin: Springer, 2015), 67.

[90] See "Harmonisation of Trips-Plus Ipr Policies and Potential Impacts on Technological Capability: A Case Study of the Pharmaceutical Industry in Thailand," in *ICTSD Programme on IPRs and Sustainable Development* (2006), 44.

[91] See ibid., 15-18.

[92] See ____. One of the effects of the delay is to produce a large backlog of applications. As of 2016, there were roughly 8000 pending applications, of which roughly one third were for pharmaceutical products. See "Thailand: Evergreened Patents Cause Unwarranted High Drug Prices," Make Medicines Affordable, May 8, 2018, http://makemedicinesaffordable.org/en/thailand-evergreened-patents-cause-unwarranted-high-drug-prices/.

has recently announced an innovative way of reducing the backlog: a pilot project in collaboration with the Japanese Patent Office, called the "JPO-DIP Patent Prosecution Highway." Participants in this program will be able to submit patent applications to both of the national patent offices, but designate one of them as the primary reviewer. Decisions by that first office will then be submitted to the second. Although the public description of the program does not indicate that the second office must follow the ruling by the first, it seems likely that the DIP would follow the lead of the JPO. If this does indeed occur, then the program may well achieve its stated objective of "accelerat[ing] the patent application consideration."[93]

In sum, from the standpoint of foreign pharmaceutical firms, the Thai patent regime is not ideal, but it is working. They have already been granted thousands of patents on pharmaceutical products, and more are in the offing. This has enabled them to sell their products in Thailand for high prices – and the revenues generated thereby are at least potential sources of support for research and development. On the other hand, the facts that the large majority of the patents have been issued to foreign firms, not Thai firms, and that very little of the research arguably tied to the patent system is conducted in Thailand are troubling.[94] Putting aside, for the moment, the adverse impact on employment and training within Thailand, the bias reduces the likelihood that the research will be aimed at diseases endemic in Thailand or other developing countries.

Thus far, Thailand is alone among the five countries in deploying a significant patent system to augment incentives for pharmaceutical research and development. There is, however, one form of support for R&D that all five countries provide: they permit clinical trials to be conducted using their residents. The number of companies that have taken advantage of that opportunity are substantial. As of December, 2019, the US database of clinical trials lists 236 in Malawi, 4 in Namibia, 90 in Cambodia, 53 in Bolivia, and 2,627 in Thailand.[95] The registry maintained by the WHO lists 384 in Malawi, 10 in Namibia, 129 in Cambodia, 64 in Bolivia, and a remarkable 7,016 in Thailand.[96] To be sure, some of these trials involve drugs from which the residents of these countries would benefit more than the residents of developed countries. However, many involve drugs aimed at noncommunicable conditions that are more common in developed countries. Presumably, such trials are conducted in developing countries simply because it is cheaper to do so.

3. Quality

As indicated above, governmental regulation of drug quality has two dimensions: determining which medicines may be lawfully marketed; and preventing the sale and consumption of medicines that fail quality-control standards. On paper, all five of the countries we are examining appears to be well positioned with respect to both dimensions.

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[93] See "JPO-DIP Patent Prosecution Highway," https://www.ipthailand.go.th/en/คู่มือ-คำแนะนำ-ขั้นตอน-สิทธิบัตร/item/การขอให้กรมทรัพย์สินทางปัญญาใช้ผลการตรวจสอบการประดิษฐ์ของสำนักสิทธิบัตรญี่ปุ่นเพื่อประกอบการพิจารณา.html.

[94] See Kuanpoth, "Harmonisation of Trips-Plus Ipr Policies and Potential Impacts on Technological Capability: A Case Study of the Pharmaceutical Industry in Thailand," 41-45.

[95] See https://clinicaltrials.gov (last visited December 21, 2019).

[96] See http://apps.who.int/trialsearch/ListBy.aspx?TypeListing=1 (last visited December 21, 2019).

In each country, a statute and an accompanying set of regulations creates a National Medicines Regulatory Authority (NMRA) and requires its approval before a medicine can be marketed. Those agencies are: the Pharmacy, Medicines and Poisons Board of Malawi;[97] _____.

As one might expect, none of these agencies has resources or expertise comparable to the FDA or the EMA. As a result, drug approvals in all five countries take longer – and are less reliable than in the United States or Europe.[98] The adverse impact on patient welfare is obvious.

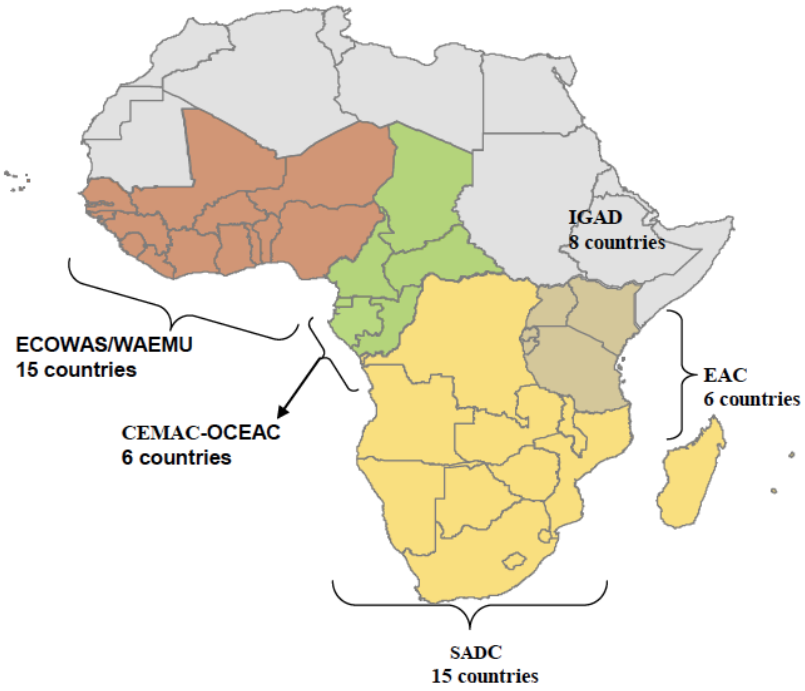
Recently, however, the governments in all subSaharan African countries have collaborated in regional organizations – all operating under the auspices of the African Medicines Regulatory Harmonization Initiative (AMRH) – to harmonize and improve their regulatory systems.[99] The relevant organizations are set forth in the map, below.

[97] The complete list of registered medicines is available at http://www.pmpb.mw/wp-content/uploads/2017/01/All-Registered-Products-30_06_17.pdf.

[98] See, e.g., Ahonkhai V, Martins SF, Portet A, Lumpkin M, Hartman D (2016) Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. PLoS ONE11(11): e0166515. https://doi.org/10.1371/journal.pone.0166515.

[99] The portal for the AMRH is https://www.nepad.org/programme/african-medicines-regulatory-harmonisation-amrh. The initiative is a programme of the African Union and has been funded and guided by a host of international organizations: Pan-African Parliament (PAP), World Health Organization (WHO), Bill and Melinda Gates Foundation, World Bank (WB), UK Department for International Development (DFID) and US Government-PEPFAR and the Global Alliance for Vaccines and Immunization (GAVI). These organizations will be discussed in more detail in section D, below.

Figure 4[100]



The harmonization has proceeded most rapidly in the East African Community (EAC), but not far behind is the Southern African Development Community (SADC), to which both Namibia and Malawi belong. The dimensions of improvement include: harmonizing technical requirements and guidelines for registration applications[101] and conducting at least portions of the review processes on regional, rather than national, levels.[102]

Two benefits of the harmonization are already apparent: the average time for regulatory approvals has dropped sharply, and the costs to pharmaceutical firms of obtaining approvals in multiple national markets is declining.[103] Anecdotal evidence suggests that the quality of the agencies' decisionmaking is also rising.

[Insert discussion of Cambodia, Haiti, and Thailand]

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[100] Source: Margareth Ndomondo-Sigonda et al., "The African Medicines Regulatory Harmonization Initiative: Progress to Date," *Medical Research Archives* 6, no. 2 (2018).

[101] One of the vehicles for harmonization on this level has been the Model Law for Medical Products Regulation, developed by the African Union. Its principal features are ___. Adopted by ___

[102] See Ndomondo; Malaria for Malaria Venture. Launch of the East African Community (EAC) Medicines Registration Harmonization (MRH) Project. Available at MV Website https://www.mmv.org/newsroom/events/launch-east-african-community-eac-medicines-registration-harmonization-mrh-project.

[103] See, e.g., Ndomondo-Sigonda et al., "The African Medicines Regulatory Harmonization Initiative: Progress to Date."; Scofield, Ian (2017) African Regulatory Harmonization Project Cuts Drug Approval Times and Saves Scarce Resources. Accessed on 20 June 2017 on URL: https://pink.pharmamedtechbi.com/PS119932/African-Regulatory-Harmonization-Project-Cuts-Drug-Approval-Times-And-Saves-Scarce-Resources;

The situation is less promising with respect to the second of the two dimensions. Although all five of the NMRAs have the authority to conduct post-marketing surveillance and to remove nonconforming medicines from the market, in practice none has the resources to do so effectively. Their staffs of inspectors are small, and none of the countries contains a WHO certified laboratory capable of reliably subjecting drug samples to HPLC testing. This is especially problematic because, as indicated above, most drugs distributed in all five countries are manufactured by companies located in India or China (or Brazil), over whose plants the NMRAs have no control. The hazards posed by unscrupulous manufacturers and importers are exacerbated by the imperfections in the imperfections in the distribution chains and storage conditions, mentioned above. With distressing frequency, even properly manufactured drugs have degraded by the time they reach patients.

The net result: the percentage of medicines that are either falsified or substandard is high. Exactly how high the rate is in each of the four countries is uncertain. As explained in the Introduction, the percentage in the developing world as a whole is over 10%. Empirical studies in the five countries on which we are concentrating suggest that, in all, the situation is at least as bad as in the typical developing country. In Malawi, one study found that 88.4% of the anti-malarial drugs tested either had too little (less than 90%) or too much (more than 110%) of the active ingredients they purported to contain.[104] Another found that 45.5% of a random sample of co-trimoxazole (a common antibiotic) failed quality-control standards.[105] The one study published to date of the situation in Namibia reported that 13.9% of the medicines sampled "did not conform to pharmacopoeial specifications."[106] Of the four countries, Cambodia has received the most systematic attention, in part because the Cambodian Ministry of Health has striven to combat falsified and substandard drugs. Unfortunately, despite the Ministry's efforts, all studies to date have reported the persistence of high rates of poor-quality drugs.[107] By contrast, the one published study on Bolivia is encouraging: the percentage of antimalarial drugs tested between 2006 and 2009 that failed

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[104] See Chikowe, I, Osei-Safo, D, Harrison, JJEK, et al. Post-marketing surveillance of anti-malarial medicines used in Malawi. 2015; Malaria Journal, 14:127. Cf. Khuluza, F, et al. (2016) "Use of thin-layer chromatography to detect counterfeit sulfadoxine/pyrimethamine tablets with the wrong active ingredient in Malawi," Malaria Journal, 15:215 (a pilot study assessing the efficacy of testing methods found one falsified and one substandard batch out of a sample of 28 batches of a common anti-malarial drug).

[105] Khuluza, F (2014) "In-vitro evaluation of the quality of Paracetamol and Co-trimoxazole tablets used in Malawi based on pharmacopoeial standards," Malawi Medical Journal, 26(2):38:41.

[106] See Nasser Mbaziira, "Registration and Quality Assurance of Arvs and Other Essential Medicines in Namibia," (USAID, 2015).

[107] See Daravuth Yang et al., "Quality of Pharmaceutical Items Available from Drugstores in Phnom Penh, Cambodia," *SOUTHEAST ASIAN J TROP MED PUBLIC HEALTH* 35, no. 3 (2004).(only 7.3% of 96 samples of aspirin "satisfied all six quality criteria); C.T. Lona, S. Phanouvongc R. Tsuyuokab, N. Nivannad, D. Socheata,, and N. Blumc C. Sokhane, E.M. Christophelf, A. Sminec, "Counterfeit and Substandard Antimalarial Drugs in Cambodia," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100 (2006).(27% of sampled antimalarials failed quality tests); Mohiuddin Hussain Khan et al., "Prevalence of Counterfeit Anthelminthic Medicines: A Cross-Sectional Survey in Cambodia," *Tropical Medicine and International Health* 15, no. 5 (2010).(4.2% of sampled anhelminthic medicines confirmed to be counterfeit); Naoko Yoshida et al., "A Cross-Sectional Investigation of the Quality of Selected Medicines in Cambodia in 2010," *BMC Phamacology and Toxicology* 15, no. 13 (2014): 4.(14.5% of 325 sampled drugs were of "unacceptable quality"); Shunmay Yeung et al., "Quality of Antimalarials at the Epicenter of Antimalarial Drug Resistance: Results from an Overt and Mystery Client Survey in Cambodia," *American Journal of Tropical Medical Hygiene* 92, no. 6 (2015): 44. (thorough study finding that 31.5% of sampled antimalarials contained either less than 85% or more than 115% of the stated API);

quality controls was modest.[108] However, in recent years a series of scandals in Bolivia involving the importation or distribution of deliberately falsified drugs suggests that the incidence remains high.[109] [Insert discussion of Thailand.]. In sum, in all five nations, the nature of the drug distribution system and the limited capacities of the regulatory authorities have contributed to a high rate of poor-quality drugs.

4. Access

As we saw, the primary technique employed by the government of the United States to increase residents' access to medicines is subsidies (direct and indirect) for health insurance policies that provide at least partial coverage for medicines. By contrast, the primary technique employed by most European countries is regulation of drug prices.

Neither of these techniques is employed to a significant extent by any of the five developing countries we are considering. As previously noted, private health insurance is available in some of the countries, but the proportions of the populations who subscribe are much lower than in the United States, and the governments do not subsidize the policies.[110] And none of the five countries limits the prices at which drugs may be sold in the private market.[111]

Instead, all five countries rely heavily on procurement to increase their residents' access to medicines. The Health ministries in all five formulate lists of "essential medicines" and then buy large quantities of those medicines -- typically from generic manufacturers, most of them located in either India or China.[112] The ministries then distribute those drugs, for free or at very low prices, to the people who need them.[113] This approach is made possible by large subsidies the ministries receive, directly or indirectly, from the governments of other nations or from NGOs. (Those subsidies will be discussed in more detail in the next section.)

An unintended but important advantage of this strategy is that it exerts downward pressure on the prices of drugs sold outside the public sector of the healthcare system. In Malawi, for example, a significant proportion of medicines (somewhere between 10% and 30%) are distributed by nongovernmental pharmacies, clinics, and hospitals. The government does not regulate the prices they charge, but the fact that most of the drugs are available for free in the public sector keeps prices at affordable levels. [114]

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[108] See Victor S Pribluda et al., "Implementation of Basic Quality Control Tests for Malaria Medicines in Amazon Basin Countries: Results for the 2005–2010 Period," *Malaria Journal* 11 (2012): 5.

[109] See, e.g., "Bolivia: Pharmaceutical Company Presses Charges Against Suspected Falsified Medicine Trafficket" (September 8, 2017), https://www.iracm.com/en/2017/09/bolivia-pharmaceutical-company-presses-charges-suspected-falsified-medicine-trafficker/; "Bolivia: Three Arrested in Santa Cruz for Selling Fake Medicines" (April 29, 2019), https://www.iracm.com/en/2019/04/bolivia-three-arrested-santa-cruz-selling-fake-medicines/; Marv Shepard, "Black Medicine: The Exploding International Trade in Counterfeit Medicine," Americas Quarterly, Summer 2010, https://www.americasquarterly.org/node/1698.

[110] See McCabe et al., "Pharmaceutical Supply in Africa," 12.

[111] Ibid., 12, 15.

[112] A partial exception is Thailand, where the GPO can and does manufacture many of the drugs itself.

[113] McCabe et al., "Pharmaceutical Supply in Africa," 12.

[114] Ibid.

In addition, Thailand employs another technique for increasing access. As indicated above, Thailand is alone in having a robust patent system for pharmaceutical products. It is also alone, however, it being willing to impose compulsory licenses on patentees when necessary to ensure its residents' access to the drugs at issue. This technique will figure significantly in our proposals for reform, so Thailand's usage of it merits discussion in detail.

First, some background: Article 31 of the TRIPS Agreement (which, as we have seen, binds all member countries of the World Trade Organization) imposes significant limitations on countries' ability to force patentees to license other parties to use patented technologies.[115]

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[115] Article 31 provides:

Where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:

(a) authorization of such use shall be considered on its individual merits;

(b) such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly;

(c) the scope and duration of such use shall be limited to the purpose for which it was authorized, and in the case of semi-conductor technology shall only be for public non-commercial use or to remedy a practice determined after judicial or administrative process to be anti-competitive;

(d) such use shall be non-exclusive;

(e) such use shall be non-assignable, except with that part of the enterprise or goodwill which enjoys such use;

(f) any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use;

(g) authorization for such use shall be liable, subject to adequate protection of the legitimate interests of the persons so authorized, to be terminated if and when the circumstances which led to it cease to exist and are unlikely to recur. The competent authority shall have the authority to review, upon motivated request, the continued existence of these circumstances;

(h) the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization;

(i) the legal validity of any decision relating to the authorization of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(j) any decision relating to the remuneration provided in respect of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(k) Members are not obliged to apply the conditions set forth in subparagraphs (b) and (f) where such use is permitted to remedy a practice determined after judicial or administrative process to be anti-competitive. The need to correct anti-competitive practices may be taken into account in determining the amount of remuneration in such cases. Competent authorities shall have the authority to refuse termination of authorization if and when the conditions which led to such authorization are likely to recur;

For least-developed counties (such as Malawi and Cambodia), who will not be obliged to extend patent protection to pharmaceutical products until 2033, Article 31 for the time being is unimportant. But it limits the ability of all other members of the WTO to temper patents in the interest of public health. Between 1995 and 2001, the ambiguity of many of the terms in Article 31, combined with restrictive interpretations of those terms by the United States, discouraged almost all developing countries from employing compulsory licenses. Protests and controversies arising out of the resultant impairment of public access to crucial medicines (exemplified by the inability of South African AIDS victims to afford ARVs) eventually forced the WTO to revisit the issue. The outcome was the 2001 Declaration on the TRIPS Agreement and Public Health, commonly known as the "Doha Declaration."[116] The key provision of the Declaration was Article 5, which recognizes that each WTO Member (i) has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted, (ii) has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, and (iii) is free to establish its own patent exhaustion regime (and thus to allow parallel imports – a topic to which we will return in Chapter 4).

The Doha Declaration also recognized that WTO Members with limited pharmaceutical manufacturing capacities could face difficulties in making effective use of compulsory licenses. Article 6 instructed the Council for TRIPS to find an "expeditious solution" to this problem. A long and contentious series of negotiations ensued, eventuating in an awkward compromise. In brief, the WTO Decision of August 30, 2003 permits a compulsory license to be used to supply drugs to another country experiencing health emergencies (the definition of which was intentionally left vague) and relieves the importing country of the duty to pay the patentee adequate remuneration, but imposes on the importing county a duty to adopt "reasonable measures within [its] means" to prevent diversion of the drugs to more lucrative markets.[117]

(l) where such use is authorized to permit the exploitation of a patent ("the second patent") which cannot be exploited without infringing another patent ("the first patent"), the following additional conditions shall apply:

(i) the invention claimed in the second patent shall involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent;

(ii) the owner of the first patent shall be entitled to a cross-licence on reasonable terms to use the invention claimed in the second patent; and

(iii) the use authorized in respect of the first patent shall be non-assignable except with the assignment of the second patent.

[116] WT/MIN(01)/DEC/2 (November 20, 2001). The name comes from the fact that it was adopted at the end of the Fourth Ministerial Conference of the World Trade Organization, held in Doha, Qatar in November 2001. Formally, the Declaration has interpretive force as "subsequent practice" in the application of TRIPS in the sense of Article 31(3)(b) of the Vienna Convention on the Law of Treaties. For additional detail concerning the declaration and its background, see William Fisher and Cyril Rigamonti, "The South Africa AIDS Controversy: A Case Study in Patent Law and Policy" (2005), https://cyber.harvard.edu/people/tfisher/South%20Africa.pdf.

117 See WT/L/540 (September 2, 2003), available at https://docs.wto.org/dol2fe/Pages/FE_Search/FE_S_S009-DP.aspx?language=E&CatalogueIdList=51809,2548,53071,70701&CurrentCatalogueIdIndex=1&FullTextHash=&HasEnglishRecord=True&HasFrenchRecord=True&HasSpanishRecord=True.

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In November of 2006, soon after the collapse of the negotiations over a free trade agreement, the new military government of Thailand decided to invoke its authority under sections 51 and 52 of the Thai patent statute,[118] which it believed complied with the Doha Declaration. In rapid succession, the government issued compulsory licenses on the patents on three drugs: efavirenz, a HIV drug distributed by Merck; lopinavir/ritonavir (also known as Kaletra), an HIV drug distributed by Abbott Laboratories; and clopidogrel (also known as Plavix), a popular anti-clotting drug distributed by Sanofi-Aventis and Bristol-Meyers-Squibb. Relying on these licenses, the GPO initially imported generic versions of the drugs from India and then began manufacturing generic versions itself. The sharply lower cost of the generics in turn enabled the government to provide drugs to large sets of people in the public health sector.[119]

Both the affected firms and the government of the United States responded angrily. In their view, these compulsory licenses were illegitimate for several reasons: they were issued without adequate prior consultation, they provided the patentees insufficient remuneration; some did not involve true health emergencies, and so forth. The USTR retaliated by placing Thailand on the Section 301 "Priority Watch List" and threatening to revoke some of Thailand's trade privileges. Abbott sought to punish the Thai government by withdrawing all of Abbott's patented drugs from the Thai market. However, the government held firm, and indeed soon announced additional compulsory licenses on four cancer drugs.[120] In the end, most of the firms acquiesced, agreeing to sell the drugs in question at much lower prices, and the controversy subsided. Thereafter, the government was in a much stronger position when negotiating purchases of patented medicines.[121]

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118 Article 51 provides: "In order to carry out any service for public consumption or which is of vital importance to the defense of the country or for the preservation or realization of natural resources or the environment or to prevent or relieve a severe shortage of food, drugs or other consumption items or for any other public service, any ministry, bureau or department of the Government may, by themselves or through others, exercise any right under Section 36 by paying a royalty to the patentee or his exclusive licensee under paragraph 2 of Section 48 and shall notify the patentee in writing without delay, notwithstanding the provisions of Sections 46, 46*bis* and 47. In the circumstances under the above paragraph, the ministry or bureau or department shall submit its offer setting forth the amount of remuneration and conditions for the exploitation to the Director-General. The royalty rate shall be as agreed upon by the ministry or bureau or department and the patentee or his licensee, and the provisions of Section 50 shall apply *mutatis mutandis*."

Article 52 provides: "During a state of war or emergency, the Prime Minister, with the approval of the Cabinet, shall have the power to issue an order to exercise any right under any patent necessary for the defense and security of the country by paying a fair remuneration to the patentee and shall notify the patentee in writing without delay."

Patent Act B.E. 2522 (1979) As Amended by the Patent Act (No. 2) B.E 2535 (1992) and the Patent Act (No. 3) B.E. 2542 (1999), available at https://www.wipo.int/edocs/lexdocs/laws/en/th/th007en.html.

[119] See Kuanpoth, "Compulsory Licences in Thailand."; "Thailand Issues Compulsory Licence for Patented Aids Drug," *Bridges* 10, no. 42 (2006), https://www.ictsd.org/bridges-news/bridges/news/thailand-issues-compulsory-licence-for-patented-aids-drug.

[120] See Siraprapha Rungpry and Edward J Kelly, "Compulsory Licensing Developments in Thailand," *IP Review* (2008).

[121] See Thomas Fuller, "Thailand Takes on Drug Industry, and May Be Winning," *New York Times*, April 11, 2007.

There is little doubt that, at least in the short run, the seven compulsory licenses imposed by the Thai government had substantial health benefits. One study concluded that they resulted, within a five-year period, in "12,493 QALYs gained, which translates into quantifiable incremental benefits to society of USD132.4 million."[122] The hard question is whether such benefits can be reconciled with preservation of incentives to create new drugs. In Part II of this book, we will attempt to answer it.

[122] See Inthira Yamabhai et al., "Government Use Licenses in Thailand: An Assessment of the Health and Economic Impacts," *Globalization and Health* 7, no. 28 (2011).

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