

**Infection: The Health Crisis in the Developing World and What We Should Do About It**  
(Stanford University Press, forthcoming 2017)

**Chapter 2: Institutions<sup>3</sup>**

Chapter 1 of this book examined the set of infectious diseases that are currently rampant in developing countries and the roles that drugs do or could play in controlling those diseases. A recurring theme was the need to generate a set of vaccines and medicines that would reduce the burdens caused by those diseases – and then to make those vaccines and medicines accessible to the people who could benefit from them. How we might do that is the principal focus of the remainder of the book. This chapter provides background for our analysis by sketching the machinery currently used by governments and nongovernmental organizations to influence the development and distribution of new pharmaceutical products.

This survey will contribute to our overall analysis in two ways. First, it will reveal various levers within the complex institutional system that might be employed to redirect some of the resources managed by the system toward mitigation of the global health crisis. Second, it will highlight some defects in the system, the correction of which could help advance the same goal.

A. Dimensions

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 when 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 devote 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 screening drugs for safety and efficacy; and the task of ensuring that safe and efficacious drugs are made available to the people who need them. For

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<sup>1</sup> WilmerHale Professor of Intellectual Property Law, Harvard University.

<sup>2</sup> Assistant Professor of Law, University of California at Berkeley.

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simplicity, we will refer to these functions as the incentive function, the regulatory function, and the access function.

The following section summarizes the ways in which each of these functions is currently handled in the United States. Along the way, we will note a few respects in which the laws in other countries differ. At the conclusion of this survey, we will consider the relationships among the three dimensions. As we show, the absence of coordination among them has serious costs.

Our analysis will focus disproportionately on the imperfections in the current regime. The reason is not that we think the systems employed in the United States are fundamentally misguided. Rather, we wish to highlight features that, when constructing alternative legal systems to address the problems in developing countries, we should strive to avoid.

## 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 a special and 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.

Public goods tend to 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.<sup>4</sup> 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.<sup>5</sup>

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<sup>4</sup> 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.

<sup>5</sup> 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).

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, academic tenure, scientists’ pursuit of truth, or the pleasure of participating in collaborative creative communities).<sup>6</sup>

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 or injections that 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 can employ to offset the risk that public goods will be produced in less-than-optimal quantities. First, governments can – and sometimes do – produce public goods themselves. Classic examples are lighthouses, roads,

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<sup>6</sup> For examinations of the economics of particular public goods that emphasize one or another of these factors, see Breyer 1970; Ferrell 1995; Rai 1999; Golden 2001; Benkler 2002, 2004, 2006; Raustiala & Sprigman 2012.

and national defense. Second, governments can 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 can 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.<sup>7</sup>

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 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 \$27 billion per year on such “extramural” research (in addition to roughly \$3 billion on “intramural” research) – much more than any other nation.<sup>8</sup> That amount has been reasonably stable for some time and will probably not increase materially until the longstanding crisis in the overall budget for the federal government is resolved.<sup>9</sup> 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 his invention is granted a patent that enables him 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 as it might appear. To avoid running afoul of the so-called statutory bars and thereby forfeiting his 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 he 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

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<sup>7</sup> 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.

<sup>8</sup> Congressional Budget Office, “Research and Development in the Pharmaceutical Industry,” (2006): 27ff.

<sup>9</sup> Sally Rockey, “NIH Operations under the Sequester,” March 4, 2013, <http://nexus.od.nih.gov/all/2013/03/04/nih-operations-under-the-sequester/>.

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 11 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.<sup>10</sup>

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<sup>11</sup> for “orphan drugs” (drugs that address diseases that affect fewer than 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;<sup>12</sup> 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.<sup>13</sup>

Sometimes, these various legal regimes are redundant. For example, the five-year data-exclusivity protection for a pioneering small molecule that enjoys eleven years of useful patent protection is 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

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<sup>10</sup> See Rebecca S. Eisenberg, “The Role of the FDA in Innovation Policy,” *Michigan Telecommunications & Technology Law Review* 13(2007).

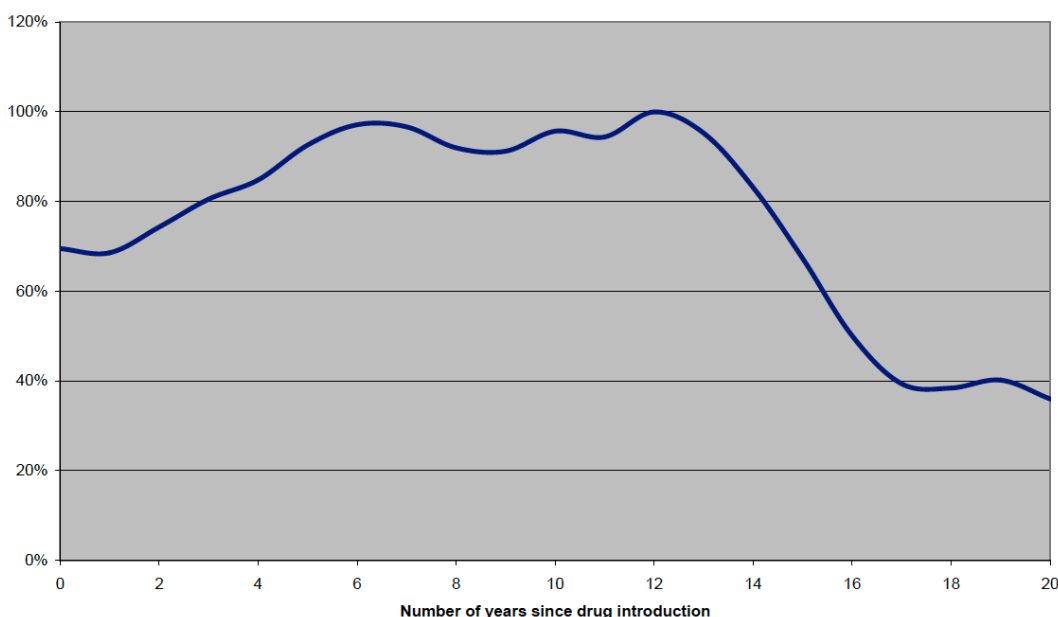
<sup>11</sup> The terms “data exclusivity” and “market exclusivity” are protean, but roughly speaking the difference between them is that data-exclusivity rules forbid the FDA to accept an application that relies upon safety or efficacy studies conducted by the beneficiary of the exclusivity, whereas market-exclusivity rules forbid the FDA to 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.

<sup>12</sup> 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).

<sup>13</sup> See Letter to FDA Commissioner Hamburg from several generic manufacturers, January 20, 2011, available at <http://www.hpm.com/pdf/generics%20biosimilars%20letter.pdf>.

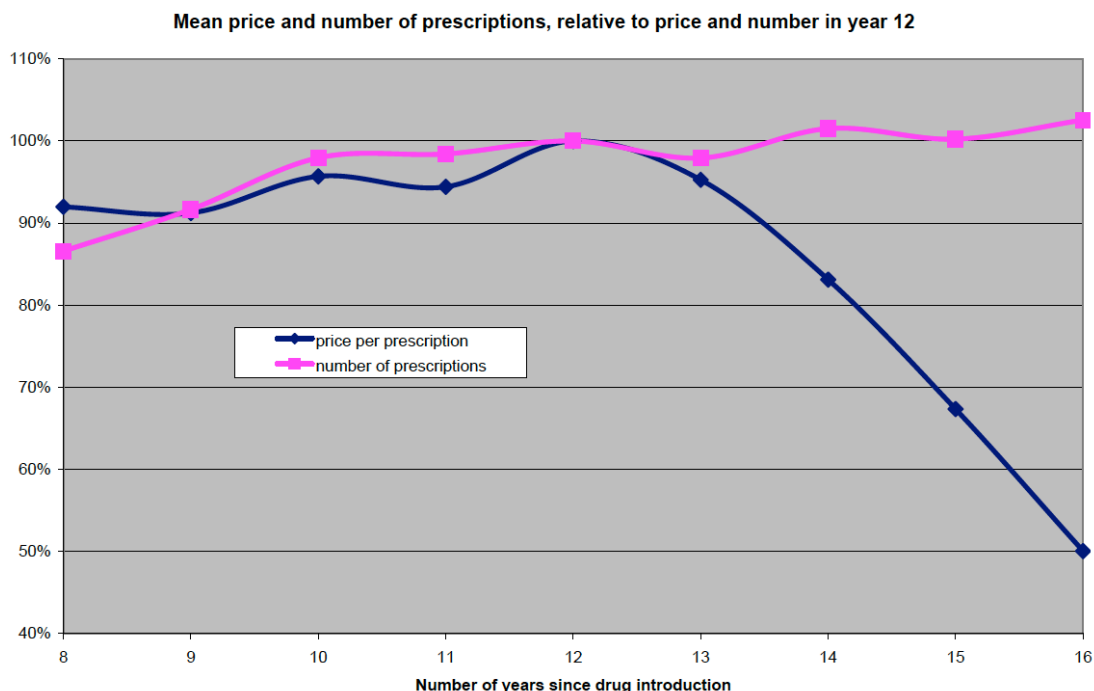
maintain high prices is provided by a recent paper by Frank Lichtenberg and Gautier Duflos.<sup>14</sup> Relying on a data set encompassing “virtually all prescription drugs sold during the period 2000-2004 in the United States,” they show that: mean generic market share remains low until 12 years after 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 free samples by the pioneer.) Details concerning the most germane of these trends are provided in the following graphs:<sup>15</sup>

**Mean drug price, relative to price in year 12**



<sup>14</sup> 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](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).

<sup>15</sup> 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 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 – a substantial portion 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. The Congressional Budget Office has estimated that the ratio between the amount the firms spend on R&D and their total sales ranges from 8% to 19%.<sup>16</sup> (Michael Scherer shows that the percentage reinvested each year varies with the prices of drugs.<sup>17</sup>) The National Science Foundation estimates that a total of roughly \$39 billion is spent each year on research and development by US pharmaceutical firms.<sup>18</sup> That number is likely a bit high, but we will use it for now.

To summarize, pharmaceutical research in the United States is supported by a combination of roughly \$30 billion of research funding by the NIH (10% intramural and 90% extramural) and by roughly \$39 billion devoted to research by pharmaceutical firms, which in turn is derived from the generous profits earned by those firms from existing drugs, profits that are enabled by a combination of legal regimes that curtail competition in the manufacture and distribution of new and improved drugs.

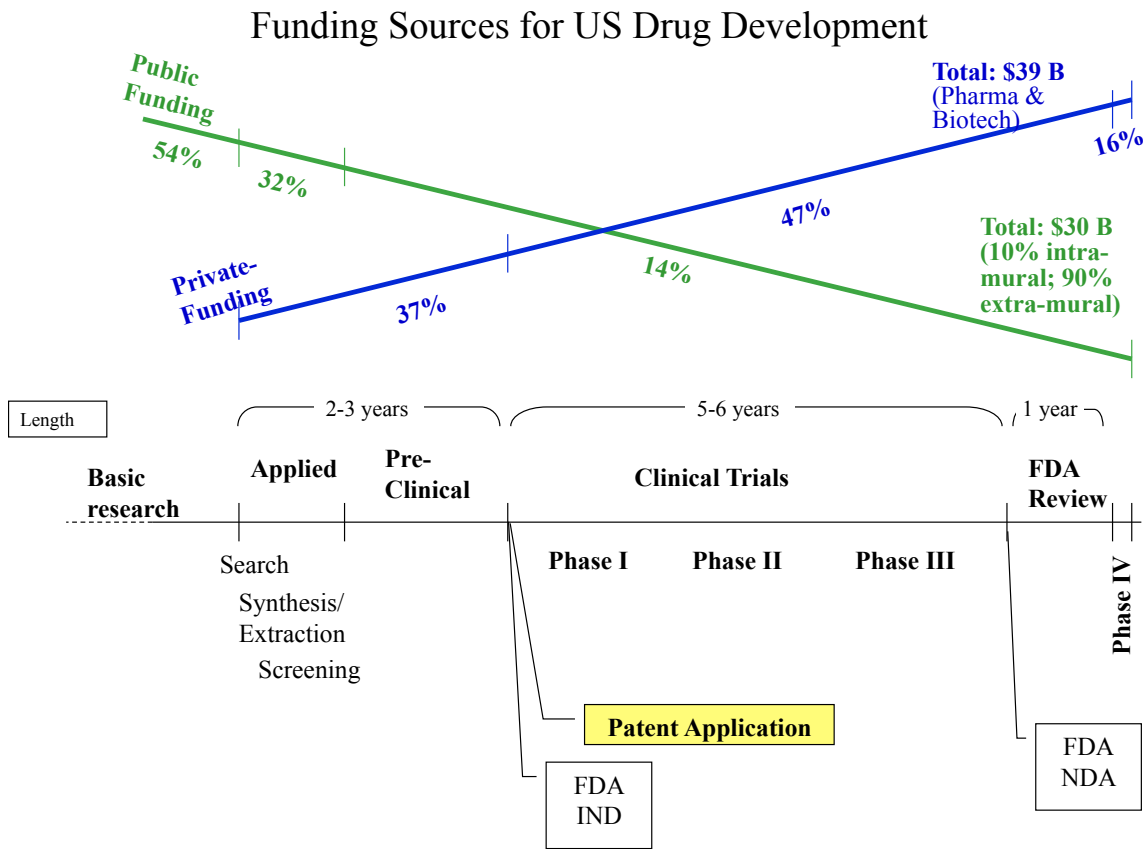
The stages of the pharmaceutical research process to which these various sums are devoted differ. Broadly speaking, primary research is funded primarily by public money,

<sup>16</sup> See Office, "Research and Development in the Pharmaceutical Industry."

<sup>17</sup> 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](http://www.wto.org/english/tratop_e/trips_e/hosbjor_presentations_e/13scherer_e.doc); ———, "The Pharmaceutical Industry -- Prices and Progress," 929.

<sup>18</sup> See Raymond M. Wolfe, "U.S. Businsss R&D Expenditures Increase in 2006; Companies' Own and Federal Contributions Rise," *National Science Foundation, Directorate for Social, Behavioral, and Economic Sciences*(2008), <http://www.nsf.gov/statistics/infbrief/nsf08313/nsf08313.pdf>.

while applied research is funded primarily by private money. The distribution in the allocation of the funds is indicated in the following chart:





## 2. Regulation

As Daniel Carpenter has shown, governments (and the US government in particular) regulate drugs more extensively and aggressively than any other product.<sup>19</sup> 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 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 the health of a few people than to aggregate benefits reaped through generating slight improvements in the health of many people;<sup>20</sup> 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, 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.<sup>21</sup>

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<sup>19</sup> Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton: Princeton University Press, 2010).

<sup>20</sup> Reasons why we might wish to make such adjustments are considered in Chapter 5.

<sup>21</sup> 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).

<b>Crisis</b>	<b>Response</b>	<b>Main Features</b>
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 <i>Johnson</i> (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 2 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.<sup>22</sup> 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).<sup>23</sup> 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 following are the most important:

- 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.<sup>24</sup>
- 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.<sup>25</sup>)
- 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.<sup>26</sup>

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<sup>22</sup> See, e.g., Mary K. Olson, "First drug launches in the U.S. and Drug Safety," in *Petrie-Flom Drugs Conference* (2009).

<sup>23</sup> Henry Grabowski and John M. Vernon, *The Regulation of Pharmaceuticals: Balancing the Benefits and Risks* (1983). 10.

<sup>24</sup> See Merrill, "The Architecture of Government Regulation of Medical Products," 1764.

<sup>25</sup> See Kevin Outterson, "The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation," *Cardozo Law Review* 31(2010).

<sup>26</sup> 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 address (or prevent recurrence of) the episodic 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.

### 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.)

Some countries rely extensively on this approach. The US government, by contrast, currently employs it infrequently. The only major procurement program currently in place in the United States is the Vaccines for Children Program, under which the federal government (specifically, the Centers for Disease 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.<sup>27</sup> 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. 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. Again, many countries rely heavily on this approach.<sup>28</sup> The United States does not. For the most part, the US government lets the market set the price for

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<sup>27</sup> See John E. Calfee and Scott Gottlieb, "Putting Markets to Work in Vaccine Manufacturing," *American Enterprise Institute for Public Policy Research* (2004).

<sup>28</sup> 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."

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.)

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 government currently 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 from both payroll taxes and income taxes employment-based health-insurance benefits. 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 increased.<sup>29</sup> 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 the United States uses to address the access issue.

### *B. Interactions*

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, 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 one 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.<sup>30</sup> Much more often, however, the failure of the

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<sup>29</sup> See Scherer 929; Weisbrod 1991 523-26; CBO4 47-48; Berndt 2010; Lackawalla.

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

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 following subsections provide examples.

## 1. Conflicts

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 in turn further worsens the “access” problem.<sup>31</sup> 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.<sup>32</sup>

The fruits of this dynamic include: 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<sup>33</sup>); and the research efforts of pharmaceutical firms focus disproportionately on diseases common in the United States.

The dynamic is no secret. In various ways, insurers (both public and private) are trying to mitigate it – for instance, by demanding the right to participate in the choice of medicines, by using their bargaining power to secure price reductions for drugs, and by adjusting co-payments to try to nudge consumers toward generic alternatives to branded drugs.<sup>34</sup> 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 47 vaccines are currently licensed for use in the United

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<sup>31</sup> 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 Competitive Marketplace," *New England Journal of Medicine* 331, no. 2 (1994).

<sup>32</sup> Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," 4-5.

<sup>33</sup> See Berndt and Newhouse, "Pricing and Reimbursement in U.S. Pharmaceutical Markets."

<sup>34</sup> See Darius Lakdawalla, "Insurer Bargaining and Negotiated Drug Prices in Medicare Part D\*," in *Petrie-Flom Drugs Conference* (2009).

States,<sup>35</sup> and the major pharmaceutical firms are investing discouragingly little money in research designed to develop new ones.

In a classic essay, Burton Weisbrod offered the following illustration of the relative merits of vaccines and cures. In the early 20<sup>th</sup> 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 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. The lesson is plain: by neglecting vaccine development, we are forgoing enormous opportunities both to alleviate suffering and to reduce costs.<sup>36</sup>

Why, then, are we neglecting vaccines? Explanations differ. Some of the factors to which some analysts point 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.<sup>37</sup> 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 helped 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

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<sup>35</sup> [Recheck this number to ensure it is current.]

<sup>36</sup> 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).

<sup>37</sup> See Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics*, no. May 2004 (2004).

signals especially unreliable.<sup>38</sup> If we had other tools at our disposal (such as a prize system) we could correct for the resultant distortion – but we don't.

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.

## 2. Gaps

Adverse interaction 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 examples are summarized below.

It is no secret that 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.”<sup>39</sup> 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) by altering 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,<sup>40</sup> but the courts in the United States have not – and are unlikely to do so. 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. A recent initiative in Europe with respect to follow-on SRIs has taken this tack, but the United States is very unlikely to follow suit. 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 regulatory regimes directs resources toward research projects that promise to generate drugs for which there are large and lucrative markets, at the expense of

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<sup>38</sup> See Michael Kremer and Rachel Glennerster, *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases* (Princeton, N.J.: Princeton University Press, 2004), 29ff.

<sup>39</sup> [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).]

<sup>40</sup> 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>.



projects that would have larger net health benefits but would generate fewer profits.<sup>41</sup> This distortion has serious adverse effects in the United States, but has even more troubling implications for developing countries. As we saw in Chapter 1, investment in vaccines and therapies aimed at the infectious diseases that plague developing countries lags far behind investment in drugs aimed at the diseases (or “lifestyle” conditions) that afflict the residents of high-income countries. How the system might be modified to reduce this distortion is addressed in Part II.

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<sup>41</sup> 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).

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