CHAPTER 7

Supply-side strategies for **tackling resistance**

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This chapter examines how changes in policies oriented toward suppliers of antibiotics, particularly drug companies, might be able to control antibiotic resistance. These policies include expansion of patent protection, loosening of antitrust restrictions, easing of regulatory hurdles to drug approval, and rewards for the discovery of new antibiotics. Two important new lessons are, first, that there are important trade-offs between demand-side and supply-side policies. Second, solutions must be tailored to the level of the externality. For example, if use of one antibiotic generates resistance to another antibiotic, not necessarily in the same chemical class, it is important to define or permit a single property right to cover both antibiotics.

The purpose of this report is to ask how the U.S. health care system might extend the effectiveness of antibiotics. Four basic strategies are available. First, limit consumer demand for antibiotics. Second, improve the efficiency of existing antibiotics. Third, improve the rationing of antibiotics by suppliers. Fourth, develop new antibiotics. Previous chapters have focused on the first two strategies. This chapter explores the last two strategies.

The goal of the third strategy, rationing, is not to limit resistance but to allocate antibiotics to those patients who value effective antibiotics the most before resistance renders all antibiotics useless. Rationing has a cross-sectional and intertemporal component. We want to administer antibiotics to individuals who truly need them not only today (e.g., to patients with bacterial infections rather than viral infections) but also over time (e.g., to patients facing a virulent new infectious disease in the future, as opposed to patients suffering common bacterial ear infections today). Rationing can be pursued with a regulatory approach that employs practice guidelines, or with a market approach that provides incentives for drug makers to allocate antibiotics to the

> Seeking to limit demand for antibiotics or to improve the efficiency of existing antibiotics reduces the returns from finding a new antibiotic.

highest-value users. We will focus on the market incentives; chapters that address consumer demand have touched upon the regulatory approach, which includes reserving new antibiotics as drugs-of-last-resort.

The fourth strategy, developing new antibiotics, faces two hurdles. One is technological: what are the prospects of finding a new molecule or method to kill or incapacitate pathogenic bacteria? The other is behavioral: how can we get researchers and drug companies to work on overcoming the technological hurdles to a new antibiotic? Because the technological hurdles are beyond the scope of this report—policy reforms cannot change biology—we focus here on behavioral obstacles.

This chapter is organized around combating resistance by improving rationing of antibiotics and by encouraging the development of new drugs. For each strategy, we discuss the various policy levers that could be employed. With respect to rationing, the obvious levers are patent law, which grants exclusive rights to market a drug, and antitrust law, which prohibits collusion in the marketing of a drug. It will be shown that these levers address efficient rationing of on-patent antibiotics but not off-patent antibiotics. To ensure proper rationing of the latter, it may be necessary to create exclusionary rights over drugs already in the public domain. With respect to developing new antibiotics, the main lever is patent law because its main goal is to spur innovation. A related lever is antitrust law. Patent law uses the carrot of a government monopoly to induce investment in research and development. Relaxing antitrust law, which cracks down on monopolies, might have a similar effect. Another lever is direct government support for research. The model could be research grants from the National Institutes of Health or awards like the X Prize, which seeks to encourage low-cost, private manned spaceflights.[1] Yet another lever is to relax Food and Drug Administration (FDA) standards for approval of new antibiotics. This would reduce the hurdles to marketing a new drug and thus raise the returns to its development. Particularly instructive are case studies of the Orphan Drug Act[2] and the Prescription Drug User Fee Acts,[3] whose goals were to spur new drug development. Before the analysis of the two strategies that are the topic of this chapter, however, the next two sections provide further background. Specifically, they offer guidance on comparing the four basic strategies for curbing resistance and discuss trends in the supply of new antibiotics.

Choosing among strategies

Ultimately, readers will have to weigh not just the different tactics for rationing or improving supply but also the different strategies—demand-side and supply-side—for controlling resistance. Although the strategies are not mutually exclusive, they can undermine one another. For example, if one seeks to limit demand for antibiotics or to improve the efficiency of existing antibiotics, one is reducing the returns from—and thus the incentives for—finding a new antibiotic.[4] The reverse

1 See http://www.xprizefoundation.com/about_us/.

2 See http://www.fda.gov/orphan/oda.htm.

3 These comprise the Prescription Drug User Fee Act (PDUFA) of 1992, later continued as PDUFA-II in 1997 and PDUFA-III in 2002. See http://www.fda.gov/oc/pdufa/.

4 See Fidler (1998), Philipson, Rubin (2004–2005), and Mechoulan et al. (2006). The Institute of Medicine's report on antimicrobial resistance

is also true: new antibiotics reduce incentives to curb the use of or extend the life of existing antibiotics.[5]

When choosing among strategies, there are two things to keep in mind. First, limiting consumer demand for antibiotics is a "no pain, no gain" strategy. Controlling the emergence of resistant bacteria requires that consumers forgo the benefits of antibiotic use. These include improvements in the health of the patient and the positive externality of limiting the spread of drug-sensitive bacteria. In contrast, strategies that focus on the supply of existing and new antibiotics do not require this tradeoff. They offer the opportunity to forestall or defeat treatable (drug-sensitive) bacterial infections without limiting the consumption of antibiotics.

Second, there may be a way to avoid the conflict between, on the one hand, limiting demand or extending the supply of existing antibiotics and, on the other hand, generating new antibiotics. The standard tool to spur innovation is patent law. Patents give drug companies monopolies so that they can charge higher prices for new antibiotics. Efforts to curb consumer demand or bolster existing antibiotics that compete with new antibiotics will limit the prices that even monopoly producers of new antibiotics can charge. That, in turn, reduces the incentive that patents provide for the development of new antibiotics. A solution is to have the government replace private demand with its own demand for new antibiotics. This could be done by directly funding research into new antibiotics or by offering prizes for new antibiotics.

To appreciate the distinctions among the four strategies for tackling resistance, it may be useful to draw an analogy with a more familiar problem: dependence on oil. Both oil and antibiotics can be thought of as nonrenewable resources. The supply of oil is finite, and the same can be said about antibiotics: when one uses an antibiotic today, one may inadvertently encourage resistance that limits other people's use of that antibiotic tomorrow.[6] A problem with nonrenewable resources is the "tragedy of the commons" (Hardin 1968). In the oil context, if two individuals can tap the same oil deposit, they will extract and sell the oil from that deposit too quickly, since if one does not take the oil, the other will. Thus, oil is sold at the marginal cost of extraction, not at a price that reflects its limited supply. The tragedy of the commons also afflicts antibiotics. If two companies can produce the same antibiotic, each will produce and sell too many doses today for fear that, otherwise, the other company will do so and bacteria will be resistant to the antibiotic tomorrow. One solution to both problems is to assign property rights (for the oil deposit, for an antibiotic molecule) to just one individual or company. The owner of the property right should internalize the consequence of finite supply and price oil or the antibiotic so as to allocate it to the highest-value users today or tomorrow. We elaborate on this connection further below.[7]

acknowledges this in the context of calls for FDA to condition approval for antibiotics on restriction on use (Harrison and Lederberg 1998). Industry sources also blame demand controls for limited supplies (Service 2004).

5 A related problem is that development of one new antibiotic reduces demand for a second new antibiotic more than in the ordinary case, where a new brand of widget reduces demand for existing brands of widgets. The reason is that a new antibiotic actually shifts the demand curve for all new antibiotics back toward the origin. The shift occurs because the new antibiotic lowers the probability of resistance to any given antibiotic. Even if a bacterium develops resistance to an existing antibiotic, the new antibiotic will kill it (Ellison and Hellerstein 1999).

6 In a previous chapter it is suggested that antibiotic effectiveness may be renewable. Because resistance has a fitness cost, it may be possible to "renew" an antibiotic by not using it for a period. During this period, nonresistant strains of bacteria may be reintroduced and, because of the fitness costs of resistance, outcompete resistant strains. Once nonresistant strains eliminate resistant strains, antibiotics will once again be useful. Nonetheless, there are two reasons to treat antibiotic effectiveness as a nonrenewable resource. First, it may take some time for nonresistant strains to return. In the short run, therefore, antibiotic effectiveness may be presumed finite. Second, when resistant strains die out, they may leave fragments of their DNA, which encode their mechanism for resistance, in the host's bloodstream. When antibiotics are used, nonresistant strains may pick up resistance not just from mutations, but also from scavenging DNA fragments in the bloodstream. As a result, after the renewal period, nonresistant strains may acquire resistance much faster than before that period. In short, renewal may eke out only a little more antibiotic resistance. When the cost of the nonuse period is factored in, the returns to renewal may be very limited.

7 A second level at which oil consumption is analogous to antibiotic use

Both the common pool problem and the pollution externality for oil have led to calls for policy reforms that resemble the four strategies for tackling resistance. One is to curb use of oil: energy conservation. The most common tactic is a gas tax. Another strategy is to extract more energy from or limit the pollution emitted from any fixed amount of oil. The usual policy levers are corporate average fuel economy (CAFE) standards and emissions limits. A third strategy might be to ration oil. This strategy has been employed to stop the common pool resource problems with oil deposits, but not to limit pollution from oil consumption. The last strategy is to develop new oil deposits and alternative sources of energy. This is implemented via tax breaks for exploration and for alternative fuels or technologies that use alternative fuels. The way in which policymakers choose among these different strategies for combating dependence on oil can guide their choice among the strategies for combating resistance.

Trends in the supply of new antibiotics

It is difficult to determine the future supply of new antibiotics. Statistical evidence suggests that the rate of innovation is lagging, yet many analysts blame this lack of innovation on the lack of substantial aggregate demand for new antibiotics. If demand is the culprit, however, then it is possible that, if aggregate demand increases then so might supply. To put it in economic terms, all one can identify when one looks at trends in investment in or applications for the approval of new antibiotics is the intersection of the aggregate demand and supply curves for new antibiotics at recent levels of demand. One cannot determine what the future supply will be, given a change—presumably a large increase—in the aggregate demand for new antibiotics. Innovation may accelerate to meet a future increase in demand because of the emergence of resistance against older antibiotics. Perhaps this optimism is unwarranted: after all, some analysts suggest that innovation takes a long time, perhaps a decade or more (Tanouye 1996; Gilcrest 2004).[8] But delays in research and development are only a concern if future increases in demand cannot be predicted. The problem for policymaking, then, is that we do not know the probability with which resistance and thus the demand for new antibiotics will unexpectedly and dramatically rise. The aim here is not to encourage readers to be optimistic about the future, but to acknowledge how little we know. With that caveat, let us turn to the data we do have.

By most accounts, the rate of innovation in antibiotics slowed in the 1980s (Travis 1994). After a series of professional conferences that sounded an alarm over resistance and highlighted the deceleration of innovation (*Science* 1994; Tanouye 1996), research and development picked up. The results, however, have been less than spectacular. Figure 7.1 graphs the number of new antibacterial agents approved in the United States between 1983 and 2005. The decline in new approvals has been both consistent and dramatic: from 16 in 1983–1987 to 7 in 1998–2002 (Spellberg, Powers et al. 2004).[9] Since then, only 4 new antibiotics have been approved (Bosso 2005). Looking forward, the picture is not much more promising. There are only 12

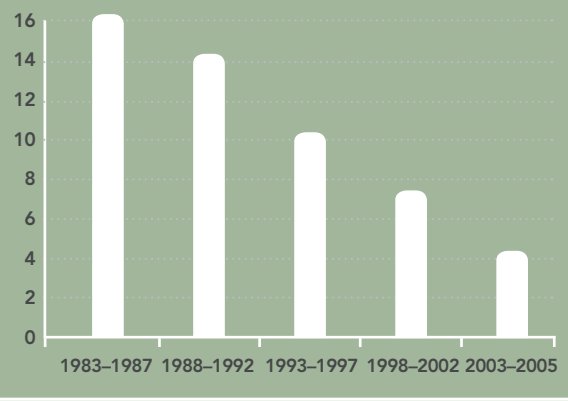
is that both have externalities. An important distinction, however, is that whereas oil consumption has a negative externality (pollution), antibiotic use has a positive externality (reducing the spread of antibiotic-susceptible bacterial infections). (The negative externality from antibiotic use does not have a distinct effect from the tragedy of the commons problem that afflicts antibiotic use.)

8 For example, the Tufts Center for Drug Development (2001) estimates it takes 10 to 15 years to bring a drug from discovery to approval for sale in the United States. This estimate is a range for all drugs, not just antibiotics.

9 For comparison, note that 225 total new molecular entities were approved by FDA from 1998 to 2002. Thus only 3 percent (7 of 225) were antibacterials. To be fair, however, it should be acknowledged that the decline in approval of new drugs is not unique to antibiotics. Submissions of new molecular entities for FDA approval fell from nearly 45 in 1996 to 25 in 2003 (FDA 2004, Figure 2). Moreover, it has been alleged that many of the drugs approved in the 1980s and 1990s were not more effective than placebos or existing drugs. If one controls for such efficacy, there may be no discernible trend in uniquely *effective* antibiotic approvals.

FIGURE 7.1

New antibacterial agents approved by FDA, 1983–2005



Sources: 1983–2002 data (Spellberg, Powers et al. 2004), 2003–2005 data (Bosso, 2005).

antimicrobial compounds beyond phase 1 studies but not yet approved by FDA (Talbot, Bradley et al. 2006, Table 2).[10] Furthermore, only a tiny fraction of new molecular entities (NMEs) in drug companies' publicly disclosed research and development programs are antibacterials. Among the world's 15 largest pharmaceutical companies, only 5 of 315 NMEs are antibacterials. At the 7 largest biotechnology companies, only 1 of 81 NMEs is an antibacterial (Spellberg, Powers et al. 2004).[11] Importantly, none of the above molecules specifically target Gram-negative bacteria.[12]

What makes matters worse is that few of these NMEs employ a novel mechanism of action. This is important because a molecule with a novel mechanism may delay the time until resistance emerges: the evolutionary adaptive response that bacteria must make to a novel mechanism is, in probabilistic terms, much more dramatic than that to an existing mechanism. A good analogy is how easily a seasoned basketball player would adjust to a change in the location of the three-point line versus how much he would have to change to play a new game, like baseball. Of the 9 new antimicrobials approved between 1998 and 2003, only 2 have novel mechanisms (Spellberg, Powers et al. 2004, Table 1). Of the 12 antimicrobials beyond phase 1 studies but not yet approved, only 2 have novel mechanisms (Talbot, Bradley et al. 2006, Table 2).

Although this picture is grim, the situation may not be as dire as the raw statistics suggest. First, many of the antibiotics currently in the research pipeline target MRSA, an important health risk (measured in aggregate dollar cost). Indeed, if the antibacterial molecules that are currently awaiting FDA approval join those recently approved, we may have several new options, and MRSA may no longer be considered as serious a mortality risk as it is now. Balanced against this is the lack of new drug development to address the untreatable infections caused by Gram-negative bacteria, such as *Escherichia coli*, *Acinetobacter baumannii*, *Enterobacter*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Second, antibiotics are an important complement to many new medical technologies, including surgical procedures, implanted medical devices, and immuno-suppressive drugs for cancer.[13] A common side effect of these technologies is

10 There are also 5 antifungals and 6 antistaphylococcal vaccines or immunoglobulins (Talbot, Bradley et al. 2006, Tables 1 and 3).

11 Recent reports by the Infectious Diseases Society of America (IDSA 2004; Talbot, Bradley et al. 2006) offer more detailed information on which new antibiotics are being developed for specific bacterial species (*Acinetobacter baumannii*, *Aspergillus*, ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, VRE, and MRSA).

12 Some antibiotic molecules are wide spectrum. And some antibiotics targeted toward Gram-positive bacteria can be combined with drugs that break down the cell walls of Gram-negative bacteria. Nevertheless, we are further behind in research on Gram-negative strains than on Gram-positive strains.

13 Antibiotics are also a complement to many existing medical technologies. Therefore, an important positive externality from improving antibiotic efficacy, whether accomplished by reducing use or by developing new antibiotics, is to improve the productivity of these medical technologies.

that they place treated patients at greater risk for bacterial infections. As more and more of these technologies emerge, there will be more demand for antibiotics, including new molecules with activity against resistant bacterial strains. This will naturally increase the return to new antibiotic development in the future.

Third, there are some promising signs on the scientific front, including research on bacteriophages, viruses that attack bacteria (Martin 2003). (This class of treatment also includes gene therapies that are administered with viruses; Cromie 2001.) Commonly used in the former Soviet bloc countries, these viruses are only now being developed in the West (Box 7.1). A phage-based antibiotic to treat *Listeria monocytogenes* in poultry was granted an experimental use permit by the Environmental Protection Agency in June 2002. But phages targeting human infections are far from obtaining FDA approval (Martin 2003). Another promising avenue of research is inhibiting the quorum-sensing ability of bacteria (Box 7.2). Certain bacteria are capable of sensing their own population density so as to optimally time their attacks or to set up defenses. If this ability could be thwarted, bacteria would be rendered less harmful or more susceptible to antibiotics.

Four itemized market factors, industry analysts suggest, are responsible for the recent lack of innovation on antimicrobials (Spellberg, Powers et al. 2004). The first is the large number of existing antibiotics, which are competitors of any new antibiotic. More than 100 antimicrobials have already been approved in the United States (Bartlett, Auwaerter et al. 2007). And a majority of bacterial infections are still caused by bacteria susceptible to existing antibiotics (Powers 2004). Even if a new drug is granted a patent, it will not be able to charge supracompetitive prices to recoup research and development costs because of these competitors. (The corollary is that when existing antibiotics fail, as in the case of MRSA, there is targeted and successful innovation.) Second, doctors tend to "reserve" new antibiotics until existing antibiotics are rendered ineffective by resistance (see also Rubin 2004–2005). Reserving delays the use of antibiotics. Even if the delay does not push the new antibiotic into the period when the developer's patent has expired, it will delay the date when the drug will begin making profits. Third, a related concern among drug companies is that doctors tend to avoid new antibiotics because of their high price tags. Doctors often have the interest of not just their patients' health but also their (or their payers') pocketbooks in mind when choosing medications. They will choose a lower-priced drug if it is nearly equally effective. This too reduces the return to companies from development of new antibiotics. Fourth, drug companies prefer to focus on treatments for chronic diseases, for market reasons. The U.S. population is aging, and older people are more likely to have chronic conditions than acute infections requiring antibiotics.[14] Moreover, patients with chronic ailments continually purchase treatment for these ailments, providing drug companies a steady source of revenue. Effective antibiotics, however, require only one course of treatment: patients are not repeat customers for the same ailment (see also Service 2004).[15]

Because this externality is probably not fully internalized by those seeking to control use of antibiotics or researching new ones, there is likely insufficient investment in promoting antibiotic effectiveness.

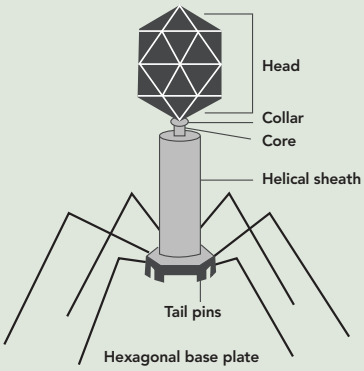
14 That said, bacterial infections often complicate chronic conditions, such as diabetes or HIV (Stinson 1996). Effective antibiotics can therefore be thought of as a useful complement to treatments for chronic conditions.

15 An analogy for the diminished incentive that drug companies have to produce antibiotics may be the diminished incentive monopolists have to produce truly durable goods. If the monopolist produces a truly durable good, present sales compete against future sales. Unless the monopolist can commit to a future price schedule or rent for its durable product, it will not be able to extract supracompetitive profits (Coase 1972). This analogy has been explored in the context of vaccine production (Kremer and Snyder 2004; Forslid 2006). But one weakness in this analogy is that patients cannot delay their consumption of an antibiotic as they can for, say, light bulbs. If patients cannot delay consumption, then future sales may not compete with existing sales.

BOX 7.1

BACTERIOPHAGES

Bacteriophages, or "bacteria eaters," were first reported as far back as 1896, but it was not until 1917 that they were identified and named by a French Canadian bacteriologist, Felix d'Herelle (Martin 2003). Bacteriophages, or phages for short, are viruses that attack bacteria. A phage has a large modular head in which it carry its genes, a tunnellike tail, and long, reedy legs used to attach to the bacterium (see image). The phage uses its tail to bore a hole into the bacterium and inject its genes. Once inside, the genes force the host into constructing new phages until the bacterium actually bursts apart, releasing hundreds of new phages (Radetsky 1996).



The promise of phages is that they are one of the most abundant life forms on the planet and readily available in the environment, and unlike antibiotics, they replicate themselves: a patient would not need repeated doses. They also have evolved to target specific bacteria, avoiding many of the complications associated with antibiotics, such as adverse reactions or the destruction of "good" bacteria, and they can mutate, which allows them to genetically evolve with the bacteria, thus reducing the likelihood of resistance. This is why d'Herelle proposed that these viruses could function as "our friend" and energetically promoted them, and in the ensuing years, phage therapy was used extensively around the world. But with the discovery of penicillin in the 1940s, research and use in the western world stopped, though it continued in Tbilisi, Georgia, at an institute that d'Herelle helped found. During that time, Russian scientists created treatments for everything from dysentery to blood poisoning to urinary tract infections, and in at least one case phages have been used as a prophylaxis (Radetsky 1996). Yet much of the research from this time period is inaccessible or classified (Braun 2006).

Today, the future of phage technology is being revived in the West; phages are being developed to destroy pathogens that infect domestic farm production animals and their environment, including aqua farms, and have also been proposed to fight bacterial infections of crops, such as citrus canker (Levin and Bull 2004). However, their greatest promise is human drug development, where advances in the biology and genetic understanding of phages (Campbell 2003) and the ability to genetically engineer phages (Westwater and Kasman 2003) have biotechnology firms racing to bring phage therapy to market as an alternative or supplement to antibiotics. Animal studies have so far proven successful (Bull, Levin et al. 2002), and although FDA has begun establishing criteria for the approval process and reviewing applications for physician investigational drug trials, which were expected to begin in late 2006 (Sulakvelidze 2006), there are still many questions that surround the efficacy and safety of phages. Actual approval of human drugs is still years away (Schoolnik, Summers et al. 2004).

—Eili Klein

BOX 7.2

QUORUM SENSING

It has long been appreciated that certain groups of bacteria are capable of interacting with each other and their surrounding environment through the use of chemical signals. Of particular interest is a specific form of cell-to-cell communication that allows bacteria to detect their own population density and express genes based on this, a method termed quorum sensing (Fuqua, Winans et al. 1994). Each species has different means of communicating, but in general, the bacteria produce a signal molecule that begins to build up in the surrounding environment. Once a specific threshold level is met, the molecule binds to and activates a receptor protein on the bacteria. The activated receptor then expresses or inhibits certain genes, which alter the bacteria cell and can induce several behaviors, including attacking the host and its production of defense mechanisms (Williams 2006). For example, *Pseudomonas aeruginosa*, a deadly human pathogen, is especially virulent because of its ability to secrete toxins, enzymes, and proteins that destroy and degrade human cells. However, the expression of these harmful exoproducts does not occur until the density of the bacteria is high (Albus, Pesci et al. 1997).

The promise of quorum sensing lies in the possibility that infections could be controlled by inhibiting the quorum-sensing capabilities of bacteria. Generally, three main avenues of approach have been recognized as points to attack the ability of bacteria to communicate: 1) blocking the production of the signal molecule; 2) inactivating or destroying the signal molecules; and 3) interfering with the receptor so as to inhibit detection of the signal molecule. Since none of these approaches interfere with or directly impede the processes of the bacteria that are essential for growth, they may not produce the harsh conditions that lead to selective pressure and resistance, as antibiotics do (Rasmussen and Givskov 2006).

Promising results have been obtained in both degrading the signal molecule and interfering with the signal receptor. In both cases, the natural world has provided clues as to how to proceed, since bacteria have been found that produce an enzyme that breaks down the signal molecule of other bacteria. And in plant trials, genetic manipulation of colonizing bacteria to express this defense was able to prevent the infection of the plant by virulent bacteria. Fungi and plants also produce a set of compounds that can inactivate the signal molecule or inhibit the signal receptor. In a promising development, these compounds, though not able to completely inhibit the quorum sensing of bacteria, have been able to attenuate the virulence of the infections, with pronounced effects on mortality (Rasmussen and Givskov 2006).

Despite the promising laboratory studies, the ability to block quorum sensing and thus control bacterial infections has not been established to work effectively in the complex environment of a living organism, and thus it will likely be years before effective treatments based on quorum sensing begin to appear.

—Eili Klein

Despite those disincentives for investment in antibiotic development, the market for antibiotics appears to be large and growing. Anti-infectives (which include antibiotics and antivirals) are the third-largest therapeutic area in terms of worldwide sales (Bush 2004, Table 4). According to BCC Research (2001), the total global market for antibiotics will cross $34.5 billion in 2006. The demand for new antibiotics in particular will be $7.4 billion and is expected to grow at an annual rate of 34 percent (Gray 2004).[16] This information is not new: even a decade ago, analysts suggested that a breakthrough antibiotic could be worth more than $1 billion per year in worldwide sales (Tanouye 1996).

Rationing existing antibiotics

Nonrenewable resources, whether oil or antibiotics, are subject to the tragedy of the commons. There are many solutions to the tragedy of the commons. Hardin (1968) stressed government regulation of consumption. Ellickson (1986) has highlighted a role for customs or traditions. But economists starting with Gordon (1954) and Coase (1960) have tended to focus on market solutions, specifically the use of property rights. If the government gives property rights over the oil deposit to one person or company, that actor will consider the opportunity cost of forgone future extraction and sale when it decides whether to extract and sell the oil today—an observation Hotelling made in a famous 1931 article on exhaustible resources. The result will be an efficient rate of extraction of the oil over time.[17]

Because an oil deposit is attached to surrounding land, defining property rights simply requires enforcing rights over access to that land. If a deposit overlaps multiple parcels of land, the law need merely permit an individual to purchase and merge the multiple parcels under her ownership.[18] Antibiotics, however, are not attached to any physical entity over which traditional property rights may be assigned. If one company produces one pill of a given antibiotic, what stops another from producing another pill of the same antibiotic? Under the current legal regime in the United States, patent law gives the owner of an antibiotic patent the exclusive right to produce the drug for sale.[19]

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Patent law is intended not to solve a commons problem but to encourage innovation.[20] As a result, there is a poor

16 In addition, there are some developmental advantages antibiotics have over drugs in other therapeutic classes. It is easier to predict whether they will be successful, they have well-defined biomarkers, clinical trials are shorter, and because the duration of therapy is shorter, there is less risk of side effects (Bush 2004; Powers 2004).

17 An important side effect of the property rights approach is that it may lead to monopoly pricing if one company is given control over an antibiotic and there are no therapeutic substitutes for that antibiotic. The result will be inefficiently low overall consumption of antibiotics (even though there will be efficient allocation of this limited consumption of the antibiotic over time and consumers). If there are antibiotics that are therapeutic substitutes for the antibiotic over which property rights are properly defined, then competition among the antibiotics will eliminate the monopoly pricing effect. In addition, the owner of the property right may use the monopoly rents to engage in more research and development than would occur in the case where there are no or incomplete property rights over the antibiotic. In that case, there is a dynamic benefit to the monopoly rents that offsets some of the costs from inefficiently low overall supply of the antibiotic.

18 An alternative to pooling the plots under one owner is to craft a unitization agreement that pools not the land but the oil revenues from all plots. The agreement then allocates these revenues across plot owners according to some measure, such as the volume of oil under each plot. This revenue sharing discourages the common pool problem by eliminating the benefits a plot owner obtains from extracting oil beyond his plot (or share of revenues). See Kim and Mahoney (2005).

19 See Brown and Gruben (1997), who argue generically that intellectual property rights can help promote preservation of product effectiveness.

20 Edmund Kitch (1977) has proposed that patent law is also intended to encourage the commercialization of an innovation—that is, investment in turning an idea into a usable product and advertising that product for sale. These activities, like innovation, are public goods that would not be optimally supplied without property rights protection. This "prospect" theory of patents intends a related but distinct role for patent law different from that discussed in this chapter. Prospect theory focuses on taking an innovation from idea to consumption. Here we consider using patent law to encourage the owner of an innovation, even after commercialization, to ration production so as to account for intertemporal consumption externalities. For antibiotics, which are like nonrenewable resources, the externality is that one person's consumption reduces the efficacy of another person's consumption.

fit between the current structure of patent law and the sort of structure necessary to avoid the commons problem with antibiotic use. For one thing, patents have limited duration. In nominal terms it is 20 years. Given the legal requirement and the time necessary to obtain FDA approval before marketing a new drug, the effective duration of a patent may be much less. One solution, proposed by Kades (2005), is to give patents over antibiotics an effectively infinite duration.

But that leaves a second issue: resistance externalities across patentable antibiotics. To analyze this issue, it is helpful to categorize antibiotics into groups not as they are currently done (by chemical classes, such as macrolides or fluoroquinolones) but based on the extent to which they trigger resistance that is also effective against other antibiotics. For clarity we shall call groups of antibiotics based on this categorization "functional (resistance) groups" or simply groups. A detailed description of the categorization may be found in Box 2.1, in Chapter 2. This categorization is useful because two antibiotics within a functional group are more likely to have negative resistance externalities on each other, even though they may belong to different chemical classes.[21] Patent law, however, may assign distinct patents to two different antibiotics within any one functional group. For example, Pfizer has a patent over extended-release azithromycin (Zithromax), and Abbott has a patent over extended-release clarithromycin (Biaxin XL). Both happen to be members of the macrolide chemical class of antibiotics. This means that even though sales of Zithromax by Pfizer may reduce the efficacy of Biaxin XL by Abbott, Pfizer and Abbott have exclusive use of their respective antibiotics.[22] One solution is for Pfizer to sell its patent rights over Zithromax to Abbott, or vice versa. But that may raise antitrust problems, which we address later in this chapter.[23] Another solution is to define patent rights not over any specific antibiotic but over all antibiotics within a functional resistance group (Laxminarayan 2001).[24]

21 In truth, any antibiotic can have a resistance externality on any other. However, the probability or seriousness of the externality rises when the two antibiotics share the same mechanism of action. In other words, the resistance externality across antibiotics is more severe within functional resistance groups, as we have defined them, than across these groups. We focus only on controlling externalities within groups because property rights also convey monopoly powers, and greater monopoly power generates potentially greater deadweight loss due to pricing. Within groups, the resistance externality may be significant enough to justify creating property rights over the entire group despite the monopoly risks. Across groups, however, the danger from externalities is not severe enough to warrant incurring the monopoly costs from creating a single property right over all antibiotics.

22 It is not obvious that the externality will always be negative. If two companies each develop an antibiotic within the same functional group, but the second is designed to overcome resistance to the first, greater production of the first antibiotic will increase demand for the second antibiotic. Whether the externality is positive or negative, however, defining property rights over the group will yield a more optimal level of rationing.

23 An advantage that patent pools have over defining broader patent rights is that the composition of the pools can change over time. This is valuable because the composition of functional resistance groups may change over time as bacteria develop new mechanisms for resisting an antibiotic. These new mechanisms may not work against certain other members of the same, preexisting functional group, and it may work against antibiotics not in the current group. We suspect that private licensing arrangements will be more flexible and responsive to these evolutionary adjustments than government allocations of patent rights.

24 A useful consequence—though one that does not motivate our proposal—of extending patent length and width would be to encourage

Even that is an incomplete solution, however, because many groups of antibiotics already exist that have either member antibiotics without patent protection or different member antibiotics whose patents are held by different companies. If a functional resistance group contains an antibiotic without patent protection, anyone can produce it. There is no way to stop the externalities from that production. If a group contains multiple patents held by different companies, again, some entity has to buy up all the patents in the group, raising antitrust problems.

A solution to the off-patent problem could be the creation of a *sui generis* ("of its own kind") right. Such a right may borrow some of the features of a right granted under patent law but does not have a basis in patent law or draw authority from the intellectual property clause in the U.S. Constitution.[25] A *sui generis* right must be adopted by Congress and may be justified by reliance on some other enumerated power of Congress, such as that granted in the commerce clause (Nachbar 2004). *Sui generis* rights are typically proposed to fill gaps in existing systems of rights. These rights have been proposed and occasionally adopted to protect semiconductor designs, databases, and biodiversity. To address the off-patent problem, a *sui generis* right over an off-patent antibiotic would borrow from patent law the feature that only the holder could produce the covered antibiotic.[26] For the reasons given above, the right should be perpetual, and the rights over all off-patent antibiotics from a given functional resistance group of antibiotics should be assigned to the same company or individual. (Different groups of off-patent antibiotics, however, could be assigned to different companies or individuals.)

The difficult question raised by a *sui generis* right over off-patent antibiotics concerns to whom the right should be assigned. The only recent example in which the U.S. government has granted a monopoly over an off-patent technology is the Orphan Drug Act (21 U.S.C. §§ 360aa–ee), which grants a seven-year period of marketing exclusivity (§360cc) for any drug, whether on patent or off, that can be used to treat an ailment that affects 200,000 or fewer persons (§360bb(a)(2)). That statute assigns the monopoly right to the company that demonstrates the efficacy of the drug for the rare disease. This is not possible with a *sui generis* right over off-patent antibiotics because anyone can demonstrate the efficacy of each antibiotic for an array of ailments. One solution may be to simply hold an auction over rights to production. An analogy would be the 1993 amendments to the Telecommunications Act of 1934 (47 U. S. C. §309(j)(1)), which, along with Federal Communications Commission regulations (e.g., In re-implementation of Section 309(j) of the Communications Act—Competitive Bidding, 9 FCC Rcd. 2348, ¶¶54, 68 (1994)), authorized the auction of radio spectrum to the highest bidders. An advantage of this approach would be that the government could extract any supracompetitive rents that the *sui generis* right might generate. Whatever the method chosen to assign *sui generis* rights over off-patent antibiotics, companies that currently produce generic versions of covered antibiotics may protest the closing of their business. They are unlikely to prevail in court, however, because it has long been settled that the government needs only to provide a "rational basis" to be allowed by courts to grant an exclusive right over off-patent technology (*Evans v. Jordan* 1813; Epstein 2002, 142). In this case, the possibility that *sui generis* rights may help control resistance externalities is that basis. Courts are therefore likely to side with the government and reject the complaints of generics manufacturers.

Even if broader and longer patents can handle externalities across future antibiotics and analogous *sui generis* rights can

innovation in antibacterials. But for reasons given later, the effect on innovation may not be very large.

25 Art. I, Sec. 8 reads, in part, "The Congress shall have Power... To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

26 What we are proposing, in other words, is a right over a currently open-access resource, viz. off-patent drugs.

handle externalities across off-patent antibiotics, how is one to address resistance across antibiotics that are currently on patent? These patents could be revoked, and whatever exclusive production and marketing rights they included could be bundled into *sui generis* rights or any future grant of broad antibiotic group patents. Because current patent holders have a property interest in their patented technology, however, the government would have to compensate the patent holders for their lost profits under the takings clause of the Fifth Amendment. If the government raised enough money by auctioning off *sui generis* rights, it might be able to afford this compensation. But given that off-patent antibiotics are much more likely to already suffer from resistance, those auctions are unlikely to raise sufficient revenue. A second problem is that revoking a legitimate patent is an unprecedented act and therefore may not be politically feasible. An alternative solution is to rely on patent holders within a functional group to sell their patents to a single company. Again, antitrust law may get in the way. Moreover, depending on one's faith in the market, one might have more or less confidence that private actors would consolidate all patents within a group (and only within a group).

Imagine if one were to overcome those hurdles. Table 7.1 summarizes policy proposals for addressing resistance externalities across hypothetical antibiotics by three types of patent status. Yet what are we to do about resistance externalities across antibiotics of different patent statuses? The answer is the same as in the previous paragraph. Extending either *sui generis* rights or future patents over all antibiotics regardless of patent status would entail a takings that would require just compensation. The alternative is to rely on licensing agreements that consolidate rights over all antibiotics from a functional resistance group, regardless of patent status, in one company (last row of Table 7.1). Consolidation, however, raises antitrust questions, to which we now turn.

:: THE ANTITRUST ISSUE

Ideally, under the "rule of reason" in U.S. antitrust cases, evaluation of the consolidation of all antibiotics within a functional group in one company should depend only on the net effect on efficiency. Simply put, the consolidation would have to meet only two conditions to pass scrutiny. First, it would have to promote economic efficiency. That is, consolidation must have some social benefit and not just redistribute wealth to producers. The resistance externalities should satisfy this condition. Second, the company must not have sufficient market power to raise the average market price of the antibiotic group. (It could raise the current price but lower the future price by implicitly shifting supply from current consumers to future consumers through rationing, but it could not raise the average for a dose across time.) The purpose of this condition is to ensure that the consolidation is used only to promote efficiency and not to generate supracompetitive rents. Although it is difficult to determine the effect of consolidation on market price, an indirect measure is to determine the effect that consolidation has on

Table 7.1 POLICY SOLUTIONS TO RESISTANCE EXTERNALITIES

PATENT STATUS	HYPOTHETICAL ANTIBIOTICS FROM A GIVEN FUNCTIONAL RESISTANCE GROUP OF ANTIBIOTICS		HORIZONTAL SOLUTION
Off-patent antibiotic	Antibiotic 1, Company A	Antibiotic 2, Company B	Perpetual *sui generis* right over both antibiotics auctioned to one company
Currently patented antibiotic	Antibiotic 3, Company C	Antibiotic 4, Company D	Antitrust exemption to allow sale of both antibiotics to one company
Future antibiotic	Antibiotic 5, Company E	Antibiotic 6, Company F	Broader, perpetual patent right covering entire group of new antibiotics
Vertical solution	Antitrust exemption to allow sale of *sui generis* and patent rights to one company		

the market share of the relevant group of antibiotics. A court might define the market narrowly to include only a specific ailment, such as staph infections, or broadly to include an array of bacteria. Regardless, there are two questions: how many other groups of antibiotics compete in that market, and what is the market share of the defendant's group? If the implied Herfindahl-Hirschman Index over market shares for competing functional groups is sufficiently low,[27] then the second condition will be met. To summarize, if one functional group of antibiotics competes with a sufficient number of other such groups of antibiotics, consolidation will be allowed. (If markets are defined narrowly, this analysis will be repeated for each relevant bacterial infection. If, on balance, the efficiencies from managing resistance outweigh the inefficiencies from market concentration across markets, the consolidation should be permitted.) If this condition is not met, the consolidation will be prosecuted as either a contract in restraint of trade under Section 1 of the Sherman Act, 15 U.S.C. §1, or as an attempt to monopolize under Section 2 of that act. It is less than obvious that the efficiencies will favor consolidation. But if they do not, perhaps it is not worth controlling resistance in the first place (at least through consolidation).

Unfortunately, consolidation of patents might not be evaluated under the rule of reason. Courts might not understand the resistance externality, be able to analyze the bacterial markets in which antibiotics compete, or trust private firms with rationing to control resistance. Worse, instead of analogizing to the case of vertical arrangements between complementary products (complementary because of the externalities), the courts might analogize to the case of horizontal arrangements (horizontal because antibiotics within a functional group may compete with one another). More precisely, courts might rule that patent holders' selling all patents to one company accomplishes the same result as patent holders' simply colluding to set prices or divide markets for their patents. Continuing the logic, because collusion is per se illegal under *U.S. v. Socony-Vacuum Oil Co.* (1940), so is consolidation.

What is the implication? Because the rule of reason may not apply to—let alone protect—consolidation, it would likely be necessary for Congress to carve an exception to antitrust enforcement against consolidation of antibiotic

27 The Herfindahl-Hirschman Index (HHI) is the sum of squared market shares of functional groups. Here, market shares are defined by bacterial infection and context (outpatient, inpatient, surgical site, lung, blood, etc.), not antibiotic or antibiotic group. The minimum HHI is zero, and the maximum is one. The higher the HHI, the higher the degree of market concentration and thus market power.

patents within a functional resistance group. Models for the exemption include those for agricultural cooperatives (Capper-Volstead Agricultural Producers' Associations Act, 7 U.S.C. §§ 291–292), unions (Section 6, Clayton Act, 15 U.S.C. § 17), or certain joint operations among newspapers (Newspaper Preservation Act of 1970, 15 U.S.C. §§ 1801–1804). The downside is that, whether the decision is to usurp existing patent rights and pay compensation or to allow private, voluntary consolidation of patents, congressional authorization—no small hurdle—will be required.

Before turning to the strategy of stimulating the supply of new antibiotics, consider two more caveats to the strategy of rationing by assigning property rights over functional resistance groups rather than individual antibiotics. One heretofore ignored complication is health insurance. Private rationing is implemented through pricing. If the owner of an antibiotic group wants to reserve an antibiotic for a future use, then it sets the current price to a level, adjusted for the time value of money, that it thinks a future consumer would pay for that antibiotic. Any patients who value current consumption more than that level will be able to purchase a dose from the class. But if patients have health insurance, they may be insensitive to price and consume a dose today even though they do not value it at the price that the owner of the group has set. Thus health insurance may defeat private rationing via the price mechanism.[28] Another complication is that resistant bacteria travel across borders. Even if the United States were to restructure its property rights and antitrust laws to control resistance externalities across antibiotics, resistant bacterial strains may develop outside our borders in countries that have not acted to address these externalities. Those strains may spread to the United States via air travelers or commercial shippers. This would reduce the return to our own efforts at controlling resistance externalities. One solution is to seek to harmonize, by treaty, the property right and antitrust rules governing antibiotics across countries. This is no small task, but it may be an essential complement to the policy proposals developed in this section.

Stimulating new antibiotics

:: PATENT OPTIONS

An alternative to rationing existing antibiotics is to create new antibiotics, especially those that have novel mechanisms of action and thus constitute new functional groups of antibiotics. The primary mechanism to encourage such

28 That said, health insurance companies may have their own reasons and tools to control resistance. We explored these in Chapter 6.

innovation is patent law. Patent law gives the patent holder the right to bar other entities from producing for consumption or marketing a patented antibiotic. At a minimum, this right prevents other entities from free-riding on a company's innovation. In other words, it allows a company to internalize the benefits of its investment in research and development.

Internalization, however, generates investment only in proportion to the market power a patent holder possesses. If two patented antibiotics equally treat the same ailment, however, neither patent holder will be able to capture much in the way of supracompetitive profits. But it is these profits that motivate (and fund) investment in innovation. Thus patent law will do little to spur innovation where there are "dueling patents." Nor will a patent create much incentive to develop new antibiotics where that antibiotic has to compete with existing, off-patent antibiotics. Unfortunately, there are currently numerous on- and off-patent antibiotics to compete with almost any new antibiotics.

So the question becomes, is there any way to generate market power so as to stimulate investment through patent law? For obvious reasons, extending the length or breadth of new patents will do little. A new patent, however encompassing, must still compete with existing products. A more promising approach, suggested by the discussion in the previous section, would be to grant new antibiotic patent holders an antitrust exemption that would allow them to exclusively license competing antibiotics, *regardless of the functional group of antibiotic*. With this right, a new patent holder could create a monopoly through merger.

Another approach, recommended by the Infectious Diseases Society of America (IDSA 2004), is to grant a wildcard patent extension to a new antibiotic patent holder. Such an extension would allow the holder to extend for a given number of years the duration of its patent on any one other drug in its portfolio. So, for example, if Pfizer developed a new antibiotic, it would be able to extend its patent on a blockbuster drug such as Lipitor by a number of years. Presumably, this extension would give Pfizer the incentive to invest in antibiotic research an amount up to the additional profit the company might anticipate from extended sales of Lipitor without generic competition.[29] Such a wildcard extension was included in an early version of the Bioshield II bill (S. 975) proposed by Senators Joseph Lieberman and Orrin Hatch in April 2005. That extension would have granted any company that developed a countermeasure to a biological weapon a two-year extension on a patent over any other drug in its portfolio (Divis 2005). If the company had no blockbuster drugs in its portfolio, it could sell its wildcard extension to any other company. This would give every company an incentive to develop a new antibiotic that is as great as the value of the wildcard to, for example, Pfizer, since any company could sell its extension to Pfizer.

The cost of either approach—an antitrust exemption or a wildcard extension—is that using monopoly profits to induce innovation has a high cost in terms of deadweight loss on consumers. Because monopolists price above marginal cost (and even above average cost), individual consumers are denied consumption when the drug's actual cost is less than their willingness to pay. This lost opportunity is the loss of economic efficiency or deadweight loss. The more elastic consumer demand is for antibiotics (with the antitrust exemption) or for a company's blockbuster drug (with the wildcard patent extension), the greater the loss. In political markets, a proxy for this loss—at least in the case of a wildcard patent extension—is opposition from generic

29 An important concern with the wildcard extension, especially if it is tradable, is that it may give too much incentive for innovation. The investment in innovation would be as large as the additional rents from the extension, an amount that could run into many billions of dollars in the case of tradable extensions. Although antibiotic resistance has serious human costs, the current and anticipated loss in life may not be worth such a large investment. To put it another way, the investment may be better spent on other health concerns, such as heart disease or HIV. Since resources are limited, allocation of resources to combat resistant bacteria on the margin takes away from resources that could be allocated to other ailments.

drug companies. Not surprisingly, they were vocal in their opposition to Bioshield II. At first they obtained a bar on the sale of the wildcard extension (actually a bar to the acquisition of a company with a wildcard extension) (Divis 2005). They later quashed even the nontradable wildcard extension proposal altogether when the Lieberman-Hatch bill was replaced by an otherwise identical bill (originally S. 1873, S. 2564 as reintroduced on April 9, 2006) from Senator Richard Burr that omitted the wildcard extension (*FDA Week* 2005; Phillips 2005).

:: GOVERNMENT REWARDS

An alternative to using the carrot of monopoly profits to induce innovation is to employ government research subsidies, tax breaks, or prizes.[30] The argument for this approach is not that it avoids monopoly pricing of a new antibiotic,[31] but rather that it works when there are no monopoly profits to be extracted with a new antibiotic patent. This might be the case when one also employs demand-side strategies to control antibiotic use. In other words, if one wants to curb antibiotic use and at the same time spur innovation, subsidies, tax breaks, and prizes are the solution. Antitrust exemptions and wildcard patents might also spur innovation in these circumstances, but they do so at the cost of monopoly pricing outside the scope of the antibiotic that is patented.[32]

Either NIH or FDA could assume the job of administering rewards for developing new antibiotics. NIH already judges scientific merit, but it currently does this for noncommercial products and early in the development pipeline.

Research subsidies would presumably be allocated through the National Institutes of Health (NIH). Tax breaks—specifically, a tax credit for expenditures on research on antibiotics—would be administered by IRS. Either NIH or FDA could assume the job of administering rewards for developing new antibiotics. NIH already judges scientific merit, but it currently does this for noncommercial products and early in the development pipeline. FDA is better situated to conduct *ex post* evaluations of drugs but does not have the capacity to hand out large sums of money.[33]

30 For general reviews comparing rewards rather than monopoly rights to encourage innovation, see Shavell and Ypersele (2001) and Abramowicz (2003).

31 Kremer (1998) has proposed a novel alternative to the traditional patent system that addresses the problem of monopoly pricing. Under his patent buyout scheme, the government would award patents to investors and then auction off the patent to the highest bidder. The purpose of the auction is to induce an accurate private valuation of the profit stream that a patent is worth. For most patents, the government would match the highest bidder's price and sell the patented technology at marginal cost. For the remainder, the government would sell the patent to the private winner of the auction. (The purpose is to induce bidders to take the auction seriously.) There are two difficulties with applying this scheme to antibiotics. First, it solves only the monopoly pricing problem. It does not solve the incentive problem where there are competing antibiotics and thus meager profits from the patent. Second, the subset of patents that are actually sold to the highest private bidders has to be random. If it were predictable, then bidders would not take seriously auctions for patents the government ultimately intended to purchase. If the government intended to purchase all antibiotic patents, then it would not be able to value those patents accurately and thus induce optimal investment in the research behind them.

32 Of course, one must balance the deadweight loss from monopoly pricing under an antitrust exemption or patents with the inefficiencies from taxation, which is necessary to fund any research subsidy or prize.

33 More recently, Glennerster and Kremer (2000) proposed "purchase precommitments" to spur innovation. Specifically, the government would commit to purchasing a fixed (large) quantity of a product at a fixed price to induce the development of that product. This concept is very similar to an award except that the government would reduce the monopoly pricing costs of an award by reselling the units it purchased at marginal cost. Therefore,

One drawback to a subsidy, as opposed to an award, is that the government must identify the recipient company before it develops a new antibiotic and risk the possibility that the effort fails. If the government is not very good at picking winners, the cost may be large. An award, however, must be larger than a subsidy to induce any given level of investment because the award requires competing companies to bear the risk of failure. Ordinarily, one might assume that the government is quite good at bearing risk. But in this case the loss is not a financial one borne by all taxpayers—as in the case of the Federal Deposit Insurance Corporation or the Pension Benefit Guaranty Corporation—but a lost health opportunity borne by patients with resistant bacterial infections. Because patients are not particularly suited to bearing this risk, it may be that a large award is warranted. Tax breaks can be structured to behave like a subsidy (e.g., a tax credit for all research expenses) or like an award (e.g., a credit for a clinical trial or marketing expenses). Hence, the choice between subsidies or an award and tax breaks will depend on the structure of the tax break.[34]

another way to view the purchase commitment is either as an award that requires the winning firm to release its product to the public domain or as an award coupled with a purchase subsidy (Lichtman 1997).

34 An interesting but unexplored option is a variant of an award that has some of the reduced-risk properties of a subsidy: a minimum-return guarantee. Such a policy would give developers of a new antibiotic not an unconditional award but a payment if and only if the return on investment in the new antibiotic failed to reach competitive levels. If the returns did, then no payment would be made. (If each new antibiotic is guaranteed this competitive return, only the costs of developing that specific antibiotic may be used to calculate a competitive return for the antibiotic. If each new functional group of antibiotic is guaranteed a competitive return, then only the costs of research on all new antibiotics should be used to calculate a competitive return. No cross-subsidization of failed nonantibiotic drugs is necessary to encourage investment in antibiotics.) One unique advantage of this minimum-return guarantee is that taxpayers pay not for the full value of a new antibiotic, but only to the extent of the market's failure to properly value that antibiotic. One problem with the scheme, however, is that it may be difficult to calculate the return that a drug company obtains from a new antibiotic. This is related to the problem with rate regulation of public utilities, such as telephone companies. Regulated companies had an incentive to exaggerate their costs to raise rates. Drug companies would have the same incentive to trigger the minimum-return guarantee.

:: MARKETING

So far this chapter has focused on the development of a new antibiotic. But generating profit from innovation requires not just research but also marketing. The main requirement for marketing is FDA approval. FDA requires that a new drug be both safe and effective (relative to a placebo). This requires three phases of trials. The cost of trials has been estimated to be roughly $125 million per drug (DiMasi, Hansen et al. 2003). Taking into account the time value of money and other indirect expenses, the overall costs of drug approval have been estimated to be as high as $231 million (Ward 1992).[35] These costs may be a significant hurdle to the marketing of a new antibiotic, and thus to its development. One solution may be to lower the requirement for approval of a drug or to speed approval of new drugs. The latter tactic was implemented

35 If one takes into account the cross-subsidization of drugs that fail to get approval, the cost may be as high as $800 million (Powers 2004). In addition, Rubin (2004–2005) suggests that FDA appears (perhaps inadvertently) to have a lower standard for withdrawing approval for antibiotics because of adverse events.

in the Prescription Drug User Fee Acts of 1997 and 2002.[36] These acts required FDA to speed up its process of reviewing drugs and taxed drug applicants to finance the quicker review. The result was a reduction in the time required for review by 3 to 7 percent per year (Berndt, Gottschalk et al. 2006). Critics were concerned that the rapid review came at the cost of safety. Philipson, Berndt et al. (2005) examined this question and estimated that the net effect was a gain for consumers: faster approval saved 180,000 to 310,000 life-years whereas lower implicit safety standards cost at most 56,000 life-years. More importantly for our purposes, the authors estimated that the Prescription Drug User Fee Acts raised the private returns of producers, and thus incentives for innovation, by $11 billion to $13 billion. Although a similar strategy might be recommended for antibiotics, it is unclear whether review times could be significantly reduced beyond levels achieved by the legislation, which already applies to antibiotics.

Another solution could be tax breaks for the cost of obtaining FDA approval. A precedent is the Orphan Drug Act, which, in addition to granting seven years of marketing exclusivity for developers of drugs for rare ailments, also grants developers a credit toward taxes owed equal to 50 percent of clinical testing costs (26 U.S.C. §44(H)). Companies could petition FDA to classify new antibiotics as orphan drugs because, given the practice of reserving new antibiotics for patients with multidrug-resistant infections, fewer than 200,000 persons have a condition for which the drug would be employed. Alternatively, Congress could explicitly extend the act to cover all new antibiotics or adopt an analogous act exclusively for antibiotics. (The Infectious Diseases Society of America has already proposed legislative language toward this end as a modification to the Burr bill.) Depending on the level of innovation desired, Congress could raise the level of the tax credit for clinical testing costs. Research by Lichtenberg and Waldfogel (2003) suggests that the Orphan Drug Act has been relatively successful.[37] The percentage of individuals dying young from rare illnesses fell 6 percent between 1979 and 1998. During the same period, the percentage dying young from more common diseases fell only 2 percent. Thus the act may be credited with a 4 percent reduction in rare disease mortality.[38]

36 A related idea, based on a proposal by Grabowski (2003), is to allow companies to get wildcard review priority from FDA in return for developing new antibiotics. The average time taken by FDA to review a nonpriority drug is 18 months; the average time for a priority drug is just 6 months. Grabowski, Vernon et al. (2002) estimate that the value of this incentive is approximately $100 million to $300 million.

37 For a less optimistic view, see Rohde (2000).

38 Space constraints preclude discussion of all policy options for improving the supply of antibiotics, including some creative tactics. For example, because investment in the development of new antibiotics is discouraged by doctors' practice of preferring cheap generics and reserving new antibiotics, an intuitive approach would be formulary controls that do the opposite—reserve generic antibiotics. This would artificially generate demand for and thus investment in new antibiotics. There are downsides that make this option unrealistic. First, costs to patients will rise. These costs are unlikely to be proportional to the resistance externalities that individual use of antibiotics generates. Conventional economic thought holds that incentives to discourage externalities should be proportional to the externality so as not to discourage net beneficial activity. Second, reserving generics will trigger strong opposition from generics manufacturers. In part, this will reflect the first downside. But almost as importantly, it makes this option less politically feasible.

Another approach would be to develop or subsidize diagnostic tests that identify resistant infections. Such tests would make it easier to identify subjects for clinical trials of new antibiotics and thus reduce the costs of obtaining marketing approval from FDA. A risk, however, is that diagnostic tests will also limit use of antibiotics once approved. Doctors may use the tests to avoid giving new antibiotics to patients without resistant infections. This will reduce the returns from developing new antibiotics.

CONCLUSION

The purpose of this chapter was to review the theoretical costs and benefits of the different policy options to encourage pharmaceutical companies to better ration of existing antibiotics and develop new antibiotics. A fundamental question that needs to be addressed in order to move forward with any particular policy, however, is to what extent each policy will actually encourage rationing or promote development. Because no answer is currently available, this chapter closes with three basic research priorities:

1. To what extent will expanding the length and breadth of property rights (directly by the government or via collusive private contracts) encourage drug companies to reduce antibiotic sales?
2. Which policy(ies) would have the greatest impact on encouraging the development of new antibiotics?
3. What level of investment in research is required to discover a new antibiotic, especially one that uses a novel mechanism of action?

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