GETTING THE ECONOMICS WRONG CAN KILL YOU: A PROGRAM FOR DEMARKETING ANTIBIOTICS

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ABSTRACT

The development of antibiotic resistance in many virulent microbes is rapidly rendering modern medicine helpless in the face of life-threatening bacterial infections. Consequently, we are on the threshold of a return to the pre-antibiotic era. The loss of antibiotic potency is a crisis that deserves immediate attention from public policy makers and business theorists. This attention is all the more overdue because current laws and business practices are hastening the development of antibiotic resistance. The cost is being paid in lost lives. This paper shows how existing incentives encourage the pharmaceutical industry and medical practitioners to treat antibiotics as an inexhaustible rather than as an expendable strategic resource. It outlines changes in law and business practice that would extend the lives both of new antibiotics and of the people who depend upon them for survival.

INTRODUCTION

Throughout much of human history, bacterial infections were both deadly and untreatable. But the development and dissemination of antibiotic wonder drugs in the middle third of the 20th Century produced effective new treatments and widespread optimism that humanity had at last defeated its age-old microbial enemies. That optimism was premature. The potency of antibiotics is proving to be an expendable resource. The more we use antibiotics, the more bacteria develop resistance to them. A number of bacterial infections, including deadly diseases such as tuberculosis are becoming untreatable with antibiotics. And many other infections will soon become untreatable. We are, therefore, on the threshold of a return to the

pre-antibiotic era. Indeed, in the case of diseases that no longer respond to existing antibiotics, we have already gone back to the future. Thus, in 1992, 13,300 people died from antibiotic resistant infections that were curable in the mid-century antibiotic golden age (Lewis, 1995).

Nor are antibiotics themselves the only medical interventions threatened by resistance. Bacterial infections are a common side effect of virtually all surgical procedures, so those procedures become much more dangerous as treatments for infections become ineffective. And because antibiotic-resistant microbes tend to flourish in environments where antibiotics are widely used—preeminently hospitals—the safety of the entire range of sophisticated medical interventions offered in a modern hospital is being compromised. These developments which seriously threaten the well being of millions call for an energetic response from medical practitioners, pharmaceutical companies, and public policy makers.

The medical community is beginning to respond. Much has been written in the medical literature about this problem (e.g., Levy, 1995), and doctors and hospitals have adopted protocols designed to inhibit the development and spread of resistant bacteria (Stephenson, 1996). But, for reasons we discuss below, medical protocols are unlikely to solve the problem unless they are reinforced by changes in the macromarketing system that distributes antibiotics. And the necessary macromarketing changes are unlikely to occur unless changes are made in the law. This paper will discuss changes in public policy and business practice that could hasten the development of new antibiotics and slow the development of resistance to the new products, topics that have received little attention.

CURRENT MACROMARKETING SYSTEM

For the vast majority of products, a sound macromarketing system must strike a balance between two antithetical societal goals: fostering innovation and making products available to all who desire them (Arrow, 1962). These goals are antithetical because innovation is most likely to occur when there is a prospect of high prices and extraordinary profits, in other words, when the innovating firm will have a monopoly on a new product. On other hand, a product will be most widely disseminated if it is a commodity, sold by a large number of firms in a perfectly competitive market with little or no profit. We balance these competing interests with patent and trademark laws. Patents create an incentive to innovate by granting an initial monopoly on innovative products. But at some point, the patent expires and the product becomes a commodity, sold by a number of firms that compete fiercely on price. As prices fall, more people can afford the product. The innovating firm retains its brand name and any brand equity it has created by being an innovator, but consumers have access to other, generally lower priced brands or to unbranded

products. The most important public policy question in this kind of macromarket is the length of the patent. Lengthening the patent will cause innovations to occur more quickly but diffuse through the population more slowly. Shortening the patent period has the opposite effect on innovation and diffusion (Viscusi, Vernon & Harrington, 1998).

It is an axiom of the currently predominant macromarketing system that products should be widely available and widely used. Incentives for a quick and widespread dissemination of new innovations are built into existing law. The innovating firm has a strong incentive to inform the public about its new products and to push their use while its patent is in force. When the patent expires, the innovating firm's extraordinary profits give competing firms a strong incentive to enter the market quickly. The new entrants usually win market share from the established firm by offering lower prices that make the product affordable for a wider public. For radios, grain combines, electric motors, and light bulbs, these arrangements work well. But for antibiotics, they lead ultimately to disaster.

Antibiotics differ from other products in being a scarce and highly expendable resource. Radios don't become less available and effective when others purchase one. Indeed, prices decline, quality improves as more people purchase radios. But with antibiotics availability and effectiveness are reduced when others use the product. Each use of an antibiotic increases the probability that the next use will be ineffectual. And the ultimate cost is paid in lives lost. Here, the societal interest is not, as it usually is, to foster the quick dissemination and widest possible use of a new product. It is to avoid frivolous uses, reserving the product for critical cases and, thus, preserving its potency as long as possible. Expressed in the technical language of economics, the sale and use of antibiotics involve a big negative economic externality, a cost borne by a third party not immediately involved in the transaction: the purchaser of the antibiotic receives a health benefit, the pharmaceutical firm a profit, but third parties must face exposure to the antibiotic resistant microbes that develop when antibiotics are used, and they are deprived of a remedy when illness does befall them.

The two parties that might seem to be best positioned to solve this problem—doctors and pharmaceutical firms—are both inhibited from doing so by a micro/macro dilemma. In their encounters with patients, doctors often face strong pressures to prescribe antibiotics when they know that an antibiotic is not called for, e.g., when the infection is viral, and they often succumb to those pressures. The Center for Disease Control estimates that a third of all antibiotic prescriptions should not have been dispensed (Levy, 1998). Doctors succumb to these pressures because prescriptions keep their customers happy whereas instructions to pay the fee, then go home and get plenty of rest and fluids annoy them. Responding to the incentives they face, many doctors use antibiotics, in effect, as a placebo.

Pharmaceutical firms likewise have a strong incentive to push excessive use of antibiotics. As previously discussed, they have a limited period of patent protection during which they need to encourage the widest possible use of their product if they are to maximize the returns on their research investment. When their patent expires, the antibiotic will have much less value to them. Unsurprisingly, they do strongly encourage aggressive use of new antibiotics. In any case, they would have a difficult time limiting the use of an antibiotic even if, ignoring their financial interests, they wanted to. Doctors strongly resist any encroachment by pharmaceutical firms upon their prescribing prerogatives. Since doctors are unavoidable gatekeepers for the drug companies' products, these companies are unwilling to offend doctors by seeking to control their behavior. Thus, both doctors and pharmaceutical firms face incentives at the micro level that stop them from adequately addressing the macro problem of antibiotic resistance.

AN ALTERNATIVE MACROMARKETING SYSTEM

Given the micro/macro dilemmas that doctors and pharmaceutical companies face within the current macromarketing regime, changes in law will probably be necessary if medical and business practices are to be modified in such a way as to inhibit the development of antibiotic resistance. The precise nature of the changes that should be made may hinge on an important empirical question--whether antibiotics can regain their potency if they are withdrawn from the market for a period of time.

Revitalization and Recycling Option

Biological logic and some empirical evidence suggest that microbes pay a price for becoming resistant to antibiotics. To become resistant they must develop the ability to produce enzymes that either degrade the antibiotic or chemically modify it in such a way as to make it ineffective. If a bacterium has to divert part of its energies from reproduction to defending against antibiotics, it should be less virulent and, thus, less dangerous. It is less dangerous because, given time to gear up, the immune system will defeat most microbes. (Antibiotics merely slow infections long enough for the immune system to gear up for the fight.) If a bacterium sacrifices too much of its reproductive capacity in order to produce enzymes that counteract antibiotics, it may not get far enough ahead of the immune system to produce a severe illness. Unfortunately, it is already clear that some bacteria remain potent enough to kill even with the burden of making enzymes to resist antibiotics.

Another potential weakness of resistant bacteria is that they may depend on the selection pressure of the antibiotic to compete against microbes that are reproductively more potent when the antibiotic is not present, i.e., those that haven't diverted some energy to producing anti-antibiotic enzymes. If the resistant bacteria thrive only when competing bacteria are suppressed by antibiotics, it may be possible to combat them by eliminating the selection pressure on which they depend, i.e., the antibiotic. Indeed, discontinuing the use of a particular antibiotic could produce two benefits: allow nonresistant bacteria (some benign) to recover and compete with those that are resistant, and, over time, restore the potency of the discontinued antibiotic.

Fortunately, there are several broad classes of antibiotics that function in different ways and are made ineffectual by different resistance mechanisms, so it would not be necessary to withdraw all classes of antibiotics at the same time to carry out this revitalization strategy. Each class could be withdrawn from the pharmacological arsenal for some empirically determined interval that would optimally restore its potency. As one class recovered, another could be withdrawn, one would hope in an unending cycle of use and revitalization that would never leave medicine powerless in the face of a bacterial infection.

But while this option is not difficult to conceive, it would be difficult to implement. If it were done by industry agreement, it would violate antitrust laws, so the laws would have to be changed to allow collusion among competitors in this special case. Even if antitrust concerns were dealt with, it is not clear that the pharmaceutical industry would be able to agree on a schedule for withdrawing the various classes of antibiotics from the market. Large firms with product lines that include all the major classes of antibiotics would be in the best position to prosper while one antibiotic class was withdrawn from the market. But even the large firms would squabble over which class should be withdrawn first since a firm's brands are not likely to be equally strong in every class. Small firms that are dependent on one kind of antibiotic would pose a still more serious challenge. Since the continued existence of the company would be at risk were they forced to entirely withdraw from the market over an extended period of time, such companies would resist a voluntary industry agreement. Thus, special compensation for small firms or government regulation would be necessary to pursue this option.

But the discussion of these business and policy options may be moot. Unfortunately, there is some recent evidence that even if the implementation problems could be overcome, a revitalization and recycling strategy may not work. In a recent study conducted in Sweden, Bjorkman, Hughes, and Andersson (1999) found that bacteria may not lose their antibiotic resistance when the selection pressure applied by the antibiotic is removed. These researchers found, as expected, that resistant bacteria were initially less virulent than their nonresistant counterparts. But the resistant bacteria became more virulent over time, *without losing their*

resistance. After reproducing for about thirty generations in mice, the resistant strains had become at least as virulent as the nonresistant bacteria. And this happened even though the mice were not continually dosed with antibiotics to maintain selection pressure. It also happened with three different antibiotics, streptomycin, rifampicin, and nalidixic acid. And the result was replicated in test tubes. Twenty-six mutant strains were developed in the experiment and only four lost their resistance to the antibiotics as a price of regaining their virulence. If these results hold for other bacteria and antibiotics, they will mean that antibiotics are a nonrenewable resource. It would, therefore, become all the more important both to use them as sparingly as possible and to develop new antibiotics to meet future needs.

Defense Contractor Option

It is prudent to assume that Bjorkman, Hughes, and Anderson's (1999) results will be supported by future research and clinical experience. If they are, our range of options in public policy and business practice will be more limited. We may have to choose just one of two options, either massive government intervention, perhaps on the model of the Defense Department's efforts to produce military equipment, or energizing the private sector by creating an enduring property interest with its inherent incentives. In this section, we discuss the first of these two options, in the next section, the second.

Assuming that antibiotics cannot be revitalized once they lose their potency, two things must happen if we are to preserve our capacity to combat bacterial infections: we must both develop new antibiotics and slow the onset of resistance to the antibiotics we already have. It is not certain that new classes of antibiotics exist and are, thus, discoverable, but if they are, government has shown that it has the capacity to fund and direct massive research projects that aim to achieve well defined goals. It is likely that a government initiative would produce new discoveries were it undertaken. The actual discoveries might well be made by pharmaceutical firms which have much of the expertise in this kind of research, but the research could be underwritten financially by the federal government.

However, judging from the history of defense contracting, any discoveries made in this way would come at a very high price in money and regulation. Participating pharmaceutical contractors would have to learn a new way of doing business, one that emphasized bureaucratic processes designed to ensure that government money was not spent fraudulently. Indeed, much of the money allocated for the project would be spent on compliance with government mandates to provide managerial and accounting controls. Given a sufficiently large financial incentive, some pharmaceutical firms would, no doubt, shoulder the burden of transforming their cultures to meet government rather than consumer demands. But given the high

returns on investment that pharmaceutical firms have historically enjoyed, government incentives would have to be very high to induce a change. And the change in culture might have negative side effects on pharmaceutical research in other areas besides antibiotics. Returns on money invested tend to be much higher when firms have a consumer-oriented business model than when they have a government-oriented model. Thus, there are good reasons for preferring the second of the two options mentioned above, the patent and property rights option.

Patent and Property Rights Option

As previously pointed out, under the current macromarketing regime, drug companies have no incentive to preserve the potency of the antibiotics they market. Indeed, the opposite is true. They have strong incentives to encourage the quickest possible adoption and widest possible use of new products so as to get a return on their investment before their patent expires. In other words, because drug companies have only temporary protection of their property rights, they use and abuse the property in ways that are more typical of renters than of owners. If they had a permanent property right, they would market an antibiotic in ways that would extend its life and preserve its potency.

A change in law could create these new incentives and new business practices. At present, drug companies have a 20 year patent on new products they develop, though the effective patent is shorter since part of the patent period is spent testing the product and getting approval to market it. If the law were changed to make the patent perpetual, companies would change their marketing practices in ways that would maximize the useful life of the antibiotic. They would try to preclude its use in trivial cases and preserve it, rather, for use in critical cases, especially cases where life is at risk.

Given the proposed change in law, firms would probably change their marketing practices because a new strategy would be needed to maximize the return on their property. If Bjorkman, Hughes, and Anderson's (1999) conclusions are borne out--and it appears that they will be (Schrag & Perrot, 1996)--the useful life of an antibiotic may be calculated roughly in terms of a certain number of doses that can be administered before resistance develops and the drug becomes ineffective. At present, the patent holder tries to ensure that the maximum number of those doses occur during limited time when its patent is in force. Under the proposed new law, having a secure right to a return on each effective dose, the company would price and promote the product in such a way as to ensure its use only in critical cases. It would do this because patients would be prepared to pay much more for the product in the critical cases where life or basic health was at stake than in trivial cases. A thousand dollars a dose is a bargain if it saves your legs, eyes, or life. By reserving the product for these critical cases, the company would get a maximum return on each

expended dose. (The price would be set to maximize the expected value of each dose sold, so price would be affected by the company's investment opportunities, by its assessment of the pricing strategy's public relations and political consequences, and by its estimate of the likelihood that alternative treatments would be developed over the life of the drug.) The company would also take care to sell the product only in venues where it would be properly used since improper administration of the drug (patients discontinuing treatment before completing a prescribed course) would decrease the total number of effective doses. By setting the price in this way and carefully monitoring how the antibiotic was administered, the company would earn the highest possible return on its investment and, incidentally, would save the maximum number of lives.

While it has many advantages over the defense contractor approach discussed above, the patent-and-property-rights solution for the resistance problem has limitations. The new patent law would affect newly developed but not existing antibiotics. And few fundamentally new antibiotics may remain undiscovered. Properly using those already discovered is, therefore, essential. This problem of existing antibiotics could be solved by making the patent law retroactive, giving the developers of existing antibiotics renewed control and, thus, an incentive to direct each dose to its most valuable use. But a retroactive law would produce a huge windfall for original patent holders while putting the makers of generic drugs out of business. And it would provide no incentive to discover new antibiotics, one of the most important benefits of the new-product law we have proposed. So though it would save lives by reserving existing antibiotics for their highest use, retroactive patent protection would probably be politically unacceptable. (The public might accept government ownership of the patent on existing antibiotics. If a government corporation sought to maximize returns to the treasury, it too could deliver the benefit of saving as many lives as possible.)

The question of what should be done to encourage responsible use of existing antibiotics can be distinguished from the question we have treated--what can be done to ensure that newly discovered antibiotics are properly used. Still, perpetual patents are probably the best way to ensure antibiotics (whether existing or new) are put to their most valued use. If the perpetual patent option is rejected (either for new or existing antibiotics), increased regulation may be the only alternative. The FDA could, for instance, reclassify antibiotics as a Class IV drug (treating them like narcotics). Doctors and drug firms have to justify their practices in dispensing narcotics and are subject to severe penalties if they don't dispense them in appropriate ways. Similar scrutiny of distribution practices and similar penalties for misprescribing would probably result in more responsible use of antibiotics and, thereby, slow the development of bacterial resistance. But this change would be most beneficial if coupled with perpetual patents.

Another limitation of our proposed change is that it provides inadequate protection for the most important innovation--the development of a new class of antibiotics. New antibiotics provide the highest level of protection and the least initial susceptibility to resistance if they use a novel mechanism to inhibit bacteria growth, i.e., if they are a new antibiotic class. Discovering a new class of antibiotics should produce exceptional financial returns because it produces an exceptional public benefit. But innovators who create a new antibiotic class typically don't reap the full return to their innovation. Competitors evade their patent through molecular modification--making small changes that produce a chemically distinct structure but one that still works the same way as the original antibiotic, though sometimes increasing potency, reducing side effects, or providing some other small benefit. Once a competitor has developed a copycat drug in the same class, both companies will push their products as aggressively as possible to capture for themselves the returns on the new antibiotic's limited inventory of potent doses. This attribute and price competition is beneficial in most product markets but not in the antibiotic market. And it can be precluded only if the original innovator has a patent on the entire drug class. As previously noted, a company that owns the class will see that each dose is put it its highest use. Other firms will still make the usual copycat improvements, so long as they are able to patent them. They can license improvements to the firm that holds the class patent, for the useful life of the drug will generally be lengthened by improvements that increase its potency--an important benefit for the company that owns the class--and the willingness of consumers to pay a premium price for the drug will increase as side effects are reduced.

CONCLUSION

The development of antibiotic resistance is rapidly rendering modern medicine helpless in the face of life-threatening bacterial infections. Our rapid return to the pre-antibiotic era is being accelerated by business practices that flow naturally from the current macromarketing regime. A new regime granting indefinite patent protection for novel antibiotics would change the incentives that govern business practice in such a way as to lengthen the effective life of a new antibiotic and, thereby, save human lives. Given the magnitude of the threat, public policy makers should move expeditiously to change current patent law, create new incentives for business and, thereby produce a new macromarketing order for anitbiotics.

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