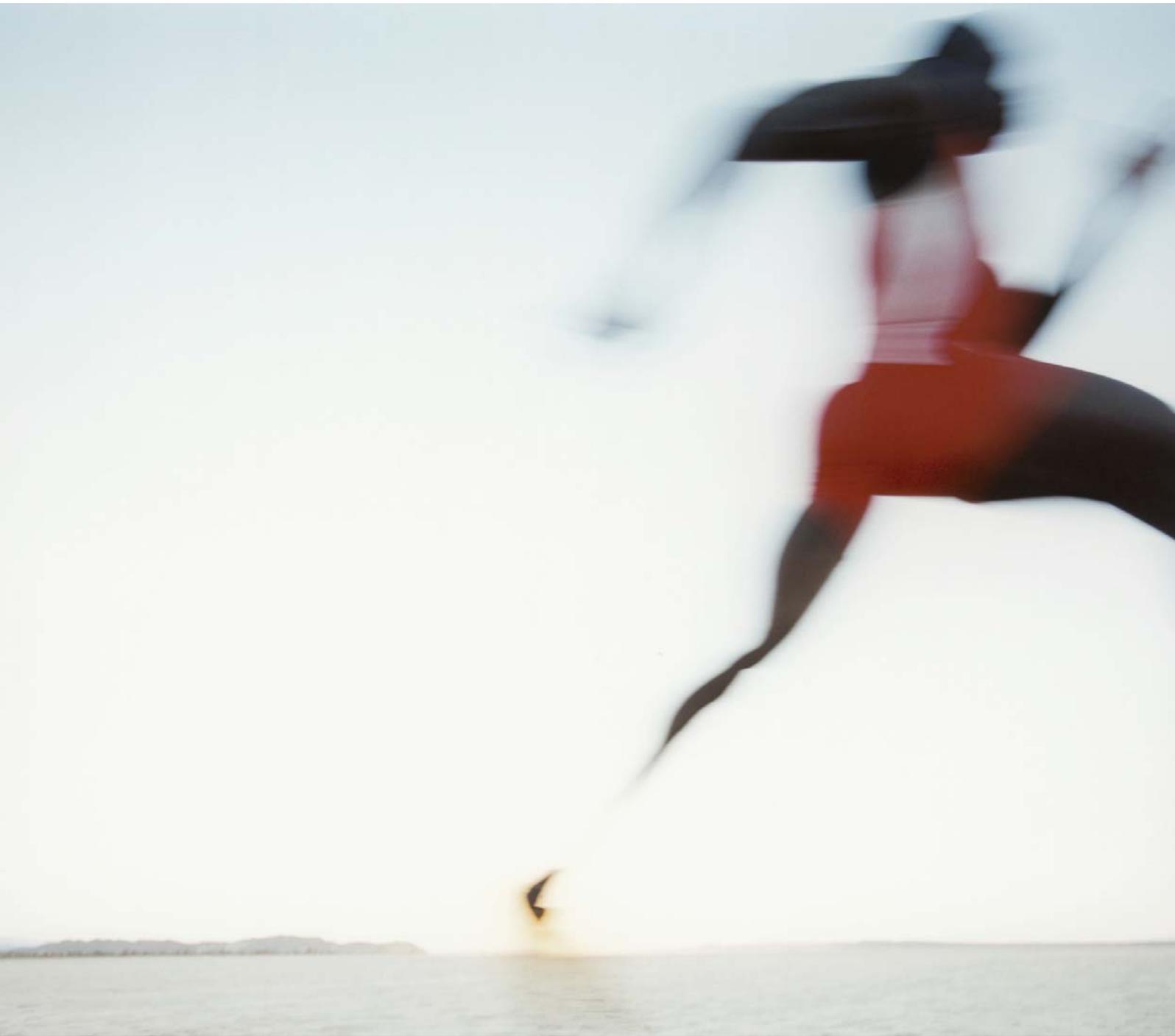


**Reducing Barriers to the Development
of High Quality, Low Cost Medicines:
A Proposal for Reforming the Drug
Approval Process**



Reducing barriers to the development of high quality, low cost medicines

A proposal for reforming the drug approval process

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Executive Summary

This paper argues that drugs are expensive not because of a lack of competition among research-based pharmaceutical companies, but because of a lack of competition in the drug approval process. Lack of competition in the drug approval process has led to exceedingly high drug development costs. High drug development costs combined with artificially low drug prices, obtained through price control legislation and legislation that eases the entry of generic products into the market, has caused lower levels of pharmaceutical research and development, innovation, and economic growth.

Estimates of the cost of developing a new drug show that these costs continue to increase, despite the recent efforts of regulatory agencies to speed up the drug-approval process. Between the years 1963 and 1975, the total cost of bringing a new drug to the market was estimated at \$119 million. Recent estimates put the cost of having a drug approved at \$802 million dollars. The dramatic rise in drug development costs is mainly explained by the increase in size and complexity of clinical trials dictated by monopoly national regulatory agencies.

We propose an alternative institutional arrangement for drug approval, whereby private drug certification bodies (DCBs) compete for assessment of the safety and efficiency of new drugs, and also grant final drug approval. The importance of reputation in maintaining clients and attracting new ones, the existence of a free press engaging in investigative journalism, and expected penalties through the legal system for corrupt and dangerous decisions by DCBs, should be sufficient to establish a well-functioning market in drug approval. Such a market in drug approval should also be effective in bringing down the costs of drug innovation as well as

prices, just as privatization has led to cost decreases, lower prices and accelerated innovation in many other sectors of the economy.

By way of analogy, we note that such a competitive market in product approval has existed for centuries among observant Jews that adhere to the laws of Kashrut (kosher food). According to Jewish Law, religious Jews are required to eat food that adheres to certain standards that are verified for compliance by religious authorities. Kashrut certification boards (KCBs) have arisen that certify Kosher food products. KCBs compete against one another and attract a following based on reputation and trust. Religious Jews can easily identify KCBs that adhere most closely to their own personal preferences for stringency. There is also a natural distribution of personal preferences for stringency within the population of religious Jews, and this distribution is reflected in the distribution of types of KCBs that operate in the market.

DCBs could similarly thrive in a drug approval market without an over-riding central regulatory agency. As in the market for Kosher food, some individuals may want an extremely safe medicine that was given approval by a known conservative DCB. Others may be less risk averse and would have the option of using a cheaper, “riskier” medicine approved by a less stringent DCB. If individuals were allowed to determine for themselves the optimal amount of safety (or stringency) required, according to their own preferences and budget constraints, the distribution of types of DCBs arising in a competitive drug approval market would likely reflect this heterogeneity, and lead to increases in consumer welfare.

As with KCBs, it is easy to imagine that DCBs, in a vigorously competitive market, would find it optimal to

build a history of good drug approvals and to develop a trustworthy relationship with their consumers. A DCB that bends to pressure from pharmaceutical companies, and which is comprised of members who are “captured” by pharmaceutical companies, would be quickly exposed. The marketability of future products would consequently suffer.

The existence of competing DCBs with no central approval agency should also reduce the R&D costs required to bring a new drug to market. Unnecessarily stringent rules and procedures for clinical tests, dictated by overly cautious central agencies, would be eliminated along with bureaucratic inefficiencies. Innovations in the drug approval process would accelerate.

Obtaining drugs at lower prices is a priority public policy issue. However, ensuring continued pharmaceutical innovation is also critical for increases in longevity, better health, higher productivity and economic growth. Balancing the price of medicine against incentives for continued drug innovation is a difficult challenge facing legislators. A promising solution to the drug-price problem is to reform the regulatory drug approval process through privatization and competition. Legislators should give serious consideration to this idea, The replacement of national drug administrations with competing DCBs, with the power of final approval, could substantially decrease the costs of drug development without compromising public health. It would lead to lower drug prices and preserve the incentives to innovate.

“The FDA has done enormous harm to the health of the American public by greatly increasing the costs of pharmaceutical research, thereby reducing the supply of new and effective drugs, and by delaying the approval of such drugs as survive the tortuous FDA process.”

Milton Friedman

I

Introduction

The price of pharmaceuticals is an issue of great concern for governments around the world. Soaring national health budgets and the fear that underprivileged populations have only limited access to life-saving medicines, have motivated policymakers to seek ways in which they can intervene in the market for pharmaceuticals. The most widespread solution that governments have adopted for lowering the price of pharmaceuticals is granting national regulatory authorities the power to violate intellectual property rights. National regulatory authorities usually permit generic firms to rely on test data, generated and paid for by innovators, in order to gain marketing authorization for their competing products.

Generic firms need only show bio-equivalence of their competing drugs in order to get marketing approval. They do not need to incur the same level of costs as the innovator in performing clinical trials. Generics can, therefore, “free-ride” on the investment of the innovator and charge a lower price upon expiration of the innovator’s patent or period of data exclusivity.

Generic penetration into the drug market has been quite successful in achieving the intended goal of lower drug prices, however, government-sanctioned violations of intellectual property rights also have their costs. Although prices in the market for pharmaceuticals have been lowered, the development costs that research-based pharmaceutical companies incur have not been reduced, thus harming the incentive for continued innovation. Policymakers are gambling that the very “visible” benefit of a lower current price for existing pharmaceutical products will outweigh the much less-visible social cost of future life-saving drugs never being introduced to the market.

This paper argues that lower prices for pharmaceutical products can be achieved without violating intellectual property rights, and without damaging the incentive to innovate. The regulatory approval process can be reformed in a way that does not compromise public health and that substantially reduces the costs incurred by innovators in gaining marketing authorization for their innovative products. Lower drug development costs and prices could be achieved through replacement of national drug administrations with competing drug certification boards. Private drug certification boards could compete on the basis of the safety, efficiency and cost of their drug approval process.

Currently, national regulatory agencies are public bodies that are far removed from the market forces of competition and legal recourse. The incentives faced by private certification boards for generating a track record of good results are likely to be stronger in a competitive certification market than the incentives faced by employees of government agencies that are enjoying relative insulation and monopoly powers (see also Campbell (1997)).

The rest of this paper unfolds as follows. Section II reviews the empirical evidence related to intellectual property protection, profits and innovation in the pharmaceutical industry. Section III describes in more detail different types of intellectual property protection and the role of generic competition. Section IV outlines the current regulatory drug approval process and quotes estimates of the increasing costs of drug approval. Section V expands upon the idea of a competitive market in drug certification among private certification boards. Section VI concludes.

II

Intellectual property, profits and innovation

New drugs are the fruit of long and costly research and development (R&D).¹ One of the most important factors that supports continued investment in R&D in the pharmaceutical industry is intellectual property protection. A well-known study by Mansfield (1994) arrives at this conclusion by surveying the R&D directors of 100 U.S. firms between the years 1981 and 1983. Respondents were asked to estimate the fraction of their inventions that would not have been developed without patent protection. The average fraction across all industries was 14%, while in the pharmaceutical industry it was 60% (see also Levin et. al. (1987) and Cohen et. al. (1997)). Taylor and Silberston (1973) found similar results in a survey of U.K. R&D-doing firms. The data indicated that in the absence of patent protection, the level of R&D investment would have been 64% lower.

These pioneering studies of the role of intellectual property rights (IPRs) in R&D activities, have raised the question, why are IPRs so much more important in the pharmaceutical industry relative to other industries? Grabowsky (2002) provides a compelling answer. He finds that IPRs are crucial in pharmaceutical innovation because of the high cost of innovation relative to the cost of imitation. Patent protection and data exclusivity provide innovators with a period of market exclusivity that allows them to recoup their large initial investments and earn a profit. Without such protection, innovative products would be quickly imitated at a very low cost, rendering the original R&D effort worthless.²

Grabowsky and Vernon (2002) offer empirical evidence on an important related point. They find that among the 118 new chemical entities (NCEs) introduced to the market between 1990 and 1994, only 30% of them had a present value of net revenue that exceeded their R&D costs. For the median drug, the cost of R&D was not

recovered. It was only among the few high selling drugs, known as blockbusters, that the return to R&D was substantial (five times greater than the return to all other drugs). This wide range of returns in new drug investment led the authors to conclude that R&D effort in the pharmaceutical industry is mainly driven by the search for a blockbuster. In fact, research-based pharmaceutical companies need to have some top selling drugs in order to cross-subsidize other R&D investments. Legislative enactments that weaken IPRs and lower the price of blockbusters, without lowering their costs of development, could cause a cascading reduction in pharmaceutical innovation.

Giacotto et al. (2003) provide empirical evidence for this latter contention in the context of price controls. They find that pharmaceutical R&D would be 30% lower were the U.S government to introduce price limits on drugs. Lowering R&D by 30% would result in 330 to 365 fewer new drugs within a twenty-year period. Price controls are widely believed to have hurt the competitiveness of pharmaceutical firms in Europe. Note that in 1992, six out of ten best selling medicines were manufactured in Europe, while in 2002 only 2 out of 10 were of European origin.

Although it seems quite clear that weaker IPRs and price controls have the consequence of discouraging pharmaceutical innovation, it is still legitimate to ask just how costly less innovation is to current and future generations. Current benefits in the form of lower prices for already existing drugs could potentially outweigh the social costs of lower pharmaceutical production in the future.

On the lower price side of the equation, The U.S. Congressional Budget Office (CBO) found that consumers did indeed save a substantial amount of

money. Consumers of pharmaceuticals saved between 8 and \$10 billion from 1990 to 1995 due to price competition from the generic industry. At introduction, generics sell, on average, at 61% of the brand name price. After two years, as more generics enter the market, generics sell, on average, at 37% of the original brand name (see Grabowski and Vernon (2000)). Importantly, however, the CBO study also found that the U.S. Hatch-Waxman Act, which eased the entry of generics into the drug market, had a significant negative impact on R&D by research-based pharmaceutical companies.

Lichtenberg (2002) directly assesses the social value of innovation in the pharmaceutical industry. He finds that pharmaceutical R&D and the introduction of new drugs significantly impact the economy through increased longevity, productivity and savings in other types of medical expenses. New drug approval in a given year increases the lifetime expectancy of people born that year by .016 years. Aggregating this number over all births in that year, as well as future births, yields a total increase of 1.2 million life-years for each yearly drug approval.

Lichtenberg estimates that for each extra dollar spent on prescription drugs, \$4.5 is gained through productivity enhancement. Furthermore, each extra dollar spent on drugs reduces other health related expenses by almost \$4. Importantly, there is a substantial rate of depreciation in the value of old drugs implying that future innovation is essential for the gains in health and wealth to be sustainable.³

III

Intellectual property rights and generic competition

IPRs in the pharmaceutical industry rely mainly on two instruments, patents and data exclusivity. Patents are usually given for 20 years from the day the patent is accepted by the national patent office. For most innovations, holding a patent is equivalent to holding a marketing authorization and market exclusivity for a certain period of time, until a newer, better alternative is introduced. For NCEs, however, having a patent can be quite disconnected from having marketing authorization. In fact, it is ten years, on average, before a newly patented medicine reaches the patient's bedside. After receiving a patent, the innovator must prove the safety and efficiency of the new drug to the regulatory authority.

In order to prove safety and efficiency of a new drug, pre-clinical and clinical tests must be performed. The results of tests on animals and humans are systematically reported in the registration dossier prepared for the regulatory authority. Because of the large investment in money and time needed to successfully gain marketing approval through clinical trials, the data generated during testing phases is kept confidential and cannot be exploited by potential competitors for a certain number of years. This protection is referred to as both data protection and data exclusivity.

Data protection is an intellectual property right that is distinct from a patent right. Some new drugs that are not patented or have an expired patent can be protected by data exclusivity. When data protection expires, a competitor can rely on the safety and efficiency tests performed by the innovator and in the possession of the regulatory authority. If the competitor can show bio-equivalence to the pioneer drug, no further tests are required. The competitor, most often generic firms, can then enter the market, saving millions of dollars in pre-

clinical and clinical trials. The significantly lower level of investment needed for a generic to gain marketing approval directly translates into a lower price for the medicine.

It is important to note that because of the high costs in time and money of gaining marketing approval from the regulatory authority, and the contentious legal environment surrounding patents, data exclusivity is becoming the dominant IP tool in the pharmaceutical industry. Increasingly stringent requirements for clinical trials have reduced the patent life of innovative drugs. According to the U.S. Federal Drug Administration (FDA), the average patent life remaining after marketing approval in 2001 was 7.8 years, instead of the original 20 years of patent protection. By contrast, other industrial sectors enjoy an average patent life of more than 18.5 years.

The last ten years have also witnessed an increase in legal patent disputes between generic and research-based pharmaceutical companies. Generics have been quite successful in challenging patents in the U.S. and in Europe and have a strong incentive to do so. In the U.S., for example, the first generic to challenge a patent is given 180 days of market exclusivity. According to the U.S. Federal Trade Commission (FTC), generics have a 75% success rate in challenging patents.

For most drugs, patent protection goes beyond data protection. However, if the testing period has been extremely long, or if the drug does not have full patent protection, data exclusivity can be the only form of IP. For example, Eprex from Jancan Cilag and Arava manufactured by Aventis had data protection beyond patent life by one and two years, respectively (see Pugatch (2004)). Taxol manufactured by Bristol-Myers Squibb (BMS) is protected only by data exclusivity. BMS

does not hold a patent since Taxol was licensed to BMS from the U.S. National Cancer Institute.

Perhaps the most important U.S. legislation that altered the role of patent protection and data exclusivity in the pharmaceutical industry is the Hatch-Waxman Act. The Hatch-Waxman Act of 1984 granted generic companies easier access to the drug market. The “Bolar” clause derived from the Hatch-Waxman Act gave generics the right to start testing bio-equivalency even before patent expiration, so that generics can enter the market almost immediately upon patent expiration.

The Hatch-Waxman Act did, however, also recognize the need to further protect market exclusivity for research-based pharmaceutical companies. The law restores part of the patent life lost by innovators in the process of obtaining marketing approval. The maximum patent life allowed under the law is 14 years regardless of the time spent on testing. A maximum of five years of patent life can be restored. Vernon and Grabowsky (1996) find that the average patent extension was 2.33 years for NCEs introduced in the first half of the 1990’s.

A Federal Trade Commission study on the impact of the Hatch-Waxman Act on competition between generics and innovators found that since passage of the Act, generic market share has grown from 19% in 1984 to 55% in 2004. It took an average of 19 months for generics to gain marketing approval between 1984–1994, and the probability of success in getting approval was very high. For brand names whose patents expired between 1994–97, generics captured 64% of the market share within a year, and 73% after two years. Prozac became a typical example of fierce generic competition. One month after generic introduction, the brand name lost 80% of its market share.

It is important to note that a significant advantage that generics have in the drug market, beyond the ability to free-ride on test data generated by innovators, is that they observe the marketability of innovative pharmaceuticals and imitate only the successful ones. This fact can be especially troublesome for the profitability of R&D. As mentioned earlier, the profits generated by blockbusters cross-subsidize many other R&D investments.

The relationship between intellectual property rights, the incentives to innovate, and competition in the pharmaceutical industry is arguably more complex in Europe than it is in the U.S. Most European countries have a national public health care system, and price controls and parallel importing are routinely used as public policy tools, especially when it comes to blockbuster drugs. Consequently, European pharmaceutical companies have substantially decreased their R&D expenditures over the past decade and are increasingly turning towards the American market for the introduction of new drugs (see Kingham and Castle (1998)).

In Europe, an innovator can gain marketing approval either at the European level, through the so-called Centralized Procedure, or through national regulatory agencies via the Decentralized Procedure. All approvals at the European level allow the innovator to market the product in all member states. This centralized procedure is mandatory for all biotech products and optional for other innovative products. At the European level, ten years of data exclusivity is granted. Interestingly, this is double the number of years of data protection offered in the U.S.

In the Decentralized Procedure, products can also gain marketing approval throughout the European Union via the Mutual Recognition Procedure (MRP). In the MRP, a marketing application is filed in a particular member state, called the Reference Member State (RMS). After gaining approval in the RMS, the innovator applies through the MRP for marketing authorization in all other member states. The approval to market the drug in other member states is not automatic and a Concerned Member State (CMS) can refuse marketing approval. In 2000, 36% of the drugs applying through the MRP did not obtain approval in at least one CMS.⁴

In the Decentralized Procedure, the innovator is granted data exclusivity that varies between six and ten years, depending on the policy of each member state.⁵ The period of data protection is essentially measured from the first marketing authorization within the EU. When data protection expires in the RMS, generic firms are allowed to file for marketing approval in that state, and through the MRP, they may gain marketing approval in other member states in which data protection has not

yet expired. Further, when data protection has expired in a particular member state, applications by generics will be accepted, even if the patent has not expired. The patent holder is responsible for bringing an action for infringement against the generic firm. These IPR rules in the Decentralized Procedure have increased the incentive of pharmaceutical companies to file marketing applications in the biggest economies first.

With the enlargement of the EU in 2003, harmonization of data protection standards among EU member states caught the attention of policymakers. The EU Council decided that the 10-year data exclusivity clause in the Centralized Procedure could be further delayed by one year if the innovator could show that the medicine is an innovative treatment. For drugs registered in the Decentralized Procedure, data exclusivity should be eight years for all member states but could be lengthened with an extra two years of market exclusivity. This rule is often referred to as the 8+2 formula. Within the two extra years, generics would be able to start the registration process, and launch their product as soon as the patent expires. The 8+2 formula was apparently motivated by the “Bolar” provision of the U.S. Hatch-Waxman Act. The European Council is hoping that these reforms will revive R&D activities of the pharmaceutical industry in Europe.

Data exclusivity has also become a central issue in international forums. In April 1994, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement was signed by member states of the World Trade Organization (WTO). Article 39.3 of the TRIPS agreement states that, *“Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.”*

The length of data exclusivity is not clearly announced in the TRIPS agreement, and this lack of definition has caused some signatories to almost totally ignore the data protection clause. For example, TEVA, the premier Israeli

generic firm, continues to enjoy liberal access to data produced by research-based pharmaceutical companies in Israel. This lack of data protection has caused a substantial reduction in R&D expenditures by research-based pharmaceutical companies in Israel, and has allowed TEVA to grow into one of the world’s largest generics manufacturer.

Current government and supra-government intervention in the pharmaceutical industry that legislates rules and exceptions to data exclusivity, has given rise to a complicated legal environment that continues to harm innovation. Policymakers need to redirect their focus on the determinants of development costs and its relationship with the institutional structure of drug approval. Lower development costs will lead to both lower prices and more innovation.

IV

The costs of the current drug approval process

The U.S. market for medicine functioned without any regulatory authority until 1938. The idea of a public regulatory authority in the U.S. arose after the appearance of a toxic drug on the market, elixir Sulfanilamide, which killed 107 people. The “thalidomide” affair in the 1960s, which led to fetal deformation when used by some pregnant women, induced the European Commission to adopt standardized regulatory assessments to assure equivalent national regulatory procedures.

The publicity surrounding the discovery of an unsafe drug in the market leads to a legitimate public outcry that engenders high political costs for national regulatory authorities. The missed gains from new medicines that are delayed or refused are more difficult to discover, so government employees have an incentive to err on the side of caution. This asymmetric situation leads regulators to allocate too many resources to the prevention of unsafe drugs. The desire to protect consumers from harmful drugs has the unintended consequence of raising the cost, and delaying or preventing the approval of new drugs.

Regulatory authorities allow new medicines or vaccines to be sold to the public only after extensive pre-clinical and clinical trials are performed. These trials examine the safety, quality and efficiency of the new drug in curing diseases. The FDA (2002) estimates that it takes, on average, 8.5 years to bring a drug to the patient’s bedside. Other estimates are substantially higher. DiMasi (1995) and Adams and Brantner (2003) estimate the duration of new drug development to be 11 and 11.3 years, respectively. These latter estimates only consider drugs that were eventually given marketing approval. Dranove and Meltzer (1994) calculate an expected duration, conditional on success, and find that it takes 13.5 years to develop a new medicine.

The drug development process is, in general, composed of four distinct stages. The first stage, pre-clinical tests, is usually conducted before the innovator files an Investigatory New Drug (IND) with the regulatory authority. Pre-clinical tests include genetic analysis and animal testing, and last 3.5 years, on average. Many drugs fail during the first stage. According to the FDA (2002), only one out of 1,000 drugs pass the pre-clinical stage.

For the few drugs that pass the pre-clinical testing stage, and review by the regulatory authority, the drug enters human clinical trials, composed of three different phases (I, II, and III). Phase I is carried out on a group of 20–80 healthy volunteers to primarily test the safety of the product. Phase II includes several hundred patients afflicted with the disease. Phase III is an extension of Phase II on a larger number of patients, usually between several hundred and a thousand.

Table 1 reports the average number of months spent in each stage, and the probability of success.

As Table 1 shows, the probability of successfully moving from one phase to the next is not monotonic. In the later phases of development, the probability of success

Table 1 **Duration and success rate for new chemical drugs⁶**

	<i>Pre-clinical</i>	<i>Phase I</i>	<i>Phase II</i>	<i>Phase III & FDA approval</i>	<i>Total</i>
Probability of success	.1%	80.7%	57.7%	56.7%	.03%
Successful duration (in months)	42	19.7	29.9	47	96.6

decreases. It is interesting to note that the length of time spent on development and the probability of success is not a function of the size of the firm. The “big-pharmas,” as measured by the number of drugs that the firm has in development, do not have an advantage over the “non-big pharmas.”⁷

After successful completion of clinical tests, the national regulatory authority must approve the new drug. This latter process lasts, on average, one year and a half.

After gaining this last approval the new medicine can be introduced to the market, although further post-approval tests must be conducted to detect adverse outcomes and long-term effects. In Europe, approved new drugs are further delayed because of the existence of government controlled health care systems. Each government has to determine the reimbursement level for each new drug, causing additional delays of several months to several years.

The length of time it takes for new drugs to enter the market, and the consequent cost to society of delays, is an issue recognized by regulatory agencies. Concern for delays has led to the passage of special legislation intended to accelerate the process. In the 1990s, the FDA adopted two new programs: “fast-track approval” which expedites review of marketing approval for drugs treating serious and life-threatening diseases, and “accelerated approval” for products that provide significant improvement over existing therapies.

Europe has also implemented similar programs. The EAEMA implemented a target time of 210 days for marketing approval of “orphan drugs” intended for the cure of rare diseases. In 2003, the goal was reached with an average approval time of 190 days. In addition, “orphan drugs” were allowed to have smaller and shorter clinical trials. In 1999, orphan drugs were approved after testing on an average sample of 588 patients. Non-orphan drugs are tested on over 5,000 patients.

Although the measures adopted by regulatory authorities in the U.S. and Europe, for a few selected products, are commendable, much further progress in shortening development times of new medicines is required. R&D requires the payment of salaries, the purchase of animals and expenses on equipment. The

firm must invest its own capital or borrow capital from external sources in order to finance its R&D activities. In either case, the length of time before commercialization directly impacts on the financing cost component of R&D activities through opportunity costs or payment of interest. Shorter development times would directly translate into lower costs and lower prices.

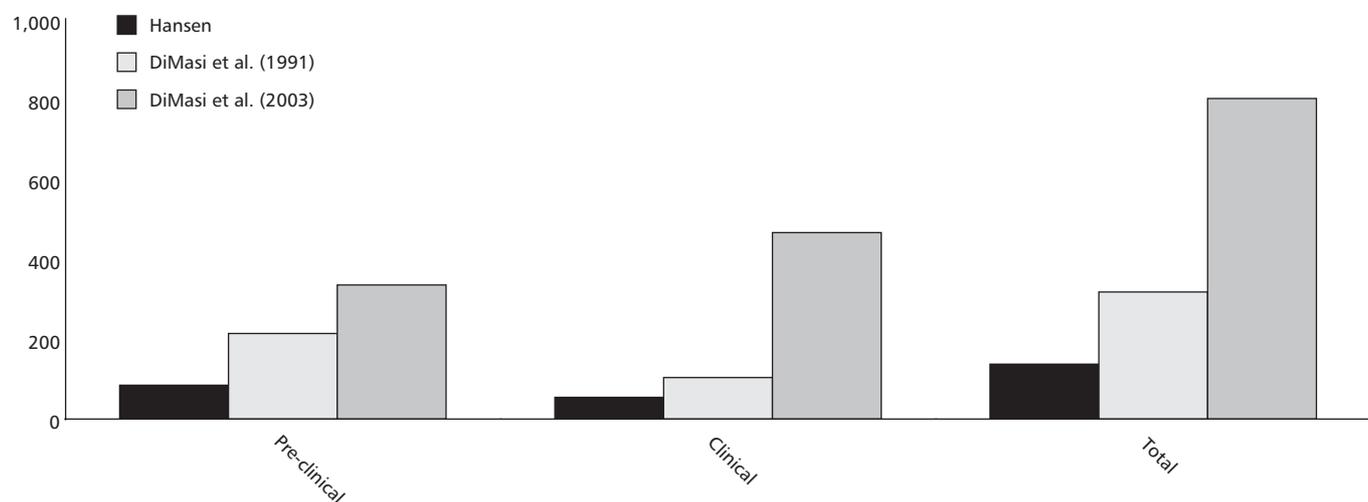
Note that the cost of developing a new drug has not decreased over time but has rather dramatically increased. An early study by Hansen (1979), using a sample of NCEs entering human testing between the years 1963 and 1975, found that the total cost of bringing a new drug to the market is \$119 million. DiMasi et al. (1991) using a similar sample between the 1970 and 1982, found the total development cost to be \$231 million, representing a 94% increase in R&D costs between the two cohorts. The Office of Technology Assessment (1993) confirmed the figures reached in these latter studies. The OTA explains the rapid rise in R&D costs in the 1970s and 1980s by increases in labor costs, the size of clinical trials and the costs of animals used in pre-clinical testing.

A more recent study by DiMasi et al. (2003) uses a random sample of 68 drugs, from 10 different pharmaceutical firms, that entered clinical testing between the years 1983 and 1994. This study uses a similar methodology as earlier studies and finds that the cost to the firm of having a drug approved is \$802 million dollars (in 2000 dollars). Including the post-approval cost of testing increases the figure to \$897 million.

DiMasi et al. also broke down the costs by development phase for their previous and current studies, and estimated the allocation of R&D resources by testing phase for the Hansen study. The results are summarized in Figure 1.

The dramatic rise in the cost of developing a new drug is mainly explained by the increase in size and complexity of clinical trials and higher labor costs. According to data compiled in the U.S. between the years 1981 and 2001, the increase in trial size was 7.47% annually (see OTA (1993), Peck (1997) and CMR (2000)). Further, clinical trial complexity rose by 4.8% annually (DataEdge, LLC (2002)). Labor costs rose because total R&D employment

Figure 1 **Estimates of capitalized pre-clinical, clinical and total costs of drug development**



increased, as did the average salaries for scientists and researchers. The Bureau of Labor Statistics projects this trend to continue over the next decade.

The exceedingly high and increasing costs of drug development, combined with artificially low market prices through price controls, and violations of intellectual property rights, places privately initiated drug innovation at risk. It is critical that policymakers consider alternative institutional arrangements for drug approval that can effectively bring down costs and prices, while preserving the incentive to innovate.

V

Toward a drug approval process based on market principles

Drug approval in the U.S. can only be achieved through the FDA. While the FDA is a pure public monopoly, the European situation is quite different. The existence of the MRP allows for a measure of competition between national regulatory authorities. A pharmaceutical company can choose the country in which to file for drug approval. Licensing fees are paid only to the first state that approves the new drug, creating an incentive for regulatory agencies in different European countries to compete. The UK, for example, streamlined its regulatory requirements under the Thatcher government and thus attracted pharmaceutical companies to seek approval there.⁸ This competitive environment gave rise to a convergence in approval times between countries. Approval times decreased in the UK and Germany by almost 70% (see Thomas et al. (1998)). The European experience demonstrates that competition among approval agencies can reduce approval times and development costs.

The current European MRP, however, faces many problems. For example, marketing approval is rarely given in all European countries. From 1998 to 2001, the number of Member States included in the MRP was, on average, less than half (Feick (2002)). Concerned States that do not receive fee payments have little incentive to accelerate approval. It may even be in the interest of Concerned States to delay approval, in the hope of signaling to the market that the Reference State was faster to approve, but fell short of insuring mutual recognition. In fact, the Decentralized Procedure took six months longer, on average, than the centralized procedure in 1999. The main component of delay in the MRP is disputes between national regulatory agencies. The European CPMP that reviews disputes continues to experience an increase in time to final decision.

The fact that mutual recognition has to be discussed and approved at many bureaucratic levels slows the overall approval process and does not foster a truly competitive environment. Moreover, national regulatory agencies still have an approval monopoly within the State. This allows the agency to strategize against other national agencies, delay approval times, and hold the citizens of the country “hostage”. A truly competitive market in drug approval among national regulatory agencies may be difficult to establish. Further devolution of drug approval to several (or many) competitive certification bodies within each state is the first-best solution.

Note that the idea of competitive certification bodies is not entirely new. For example, The Progress and Freedom Foundation (PFF) developed a detailed proposal along these lines in 1996. The PFF advanced the idea of “Drug Certification Bodies” (DCBs) that would work independently of central regulatory agencies. A national board, similar to the Joint Commission on Accreditation of Healthcare Organizations, would certify DCBs. In the PFF plan, the responsibility of final drug approval remains with the central regulatory agency. DCBs would compete in offering drug approval services to their clients (pharmaceutical companies) based on the speed of their own approvals and their quality as measured by the fraction that gain final approval from the central regulatory agency.

The PFF plan shares many similarities with the European MRP and would likely be an improvement over that system. It is different from the MRP in that one particular DCB could not prevent the marketing of a drug within a country. There would be no monopoly within a country. Although this plan would represent an improvement upon the current European structure of

monopolistic competition, it would fall short of full potential. The incentives of the central regulatory agency would still lead to an overly cautious approach to final drug approval. With this problem in mind, the FPP proposes the establishment of an independent commission that would oversee disputes between DCBs and the central regulatory authority. In other words, the FPP proposes a variation on the European CPMP. This latter aspect of the FPP proposal is its weakest link.

DCBs could be responsible not only for assessment of safety and efficiency, but also for final approval. Thus, there would be little need for a central agency with final approval powers. The safety and efficiency of drugs could be reliably determined as a result of market mechanisms and legal recourse. The importance of reputation in maintaining clients and attracting new ones, the existence of a free press engaging in investigative journalism, and expected penalties via the legal system for corrupt and dangerous decisions by DCBs, should be sufficient to establish a well-functioning market in drug approval. A well-functioning market in drug approval would be quite effective in bringing down the costs of R&D and ultimately drug prices, just as privatization has led to cost decreases, lower prices and accelerated innovation in many other sectors of the economy.

By way of analogy, it is interesting that a competitive market of this type for product approval has existed for centuries among observant Jews that adhere to the laws of Kashrut (kosher food). According to Jewish Law, certain categories of food are forbidden, meat and dairy products may not be mixed together, animals must be slaughtered in a specific way and the meat soaked and salted. Religious Jews are required to eat food that adheres to these standards and has been verified by religious authorities for compliance.

Violation of Jewish dietary restrictions may not lead to physical death, but many adherents believe that non-compliance will damage the soul. In order to aid religious Jews in their compliance, Kashrut certification boards (KCBs) have arisen that certify food products for compliance with religious standards. KCBs compete against one another and each board has its own easily identifiable label. KCBs attract a following based on

reputation and trust. Moreover, religious Jews can easily identify KCBs that adhere most closely to their own personal preferences for stringency. There is a distribution of personal preferences for stringency in requirements within the population of religious Jews, and this distribution is reflected in the distribution of types of KCBs that operate in the market.

The sustainability of KCBs for hundreds of years, spanning nations, is a good illustration of how DCBs could thrive in the absence of an over-riding central regulatory agency. Some individuals may want an extremely safe medicine that was given approval by a known conservative DCB. Others may be less risk averse and would have the option of using a cheaper, “riskier” medicine approved by a less stringent DCB.⁹

Individuals could determine the optimal amount of safety according to their preferences and budget constraints. The distribution of types of DCBs that would arise in the market would reflect this heterogeneity in the population and increase consumer welfare. Religious Jews often consult with religious leaders to choose which KCB most closely reflects their preferences for stringency. Local physicians could serve in an analogous capacity helping individuals navigate between different DCBs. It is also reasonable to assume that a market in information on DCBs would quickly arise, easing access to information and fostering transparency.

Note that KCBs have been very careful in maintaining their reputations, and fraud has rarely been a problem in that market. A KCB that misleads its consumers goes out of business quickly.¹⁰ Today there are more than 100 KCBs as well as magazines that report changes in KCB standards and possible corruption.

It is easy to imagine that DCBs, in a vigorously competitive market, would likewise find it optimal to build a good history of drug approval and to develop a trustworthy relationship with consumers. A DCB that bends to pressure from pharmaceutical companies, and which is comprised of members who are “captured” by pharmaceutical companies, would likely be quickly exposed. The marketability of the pharmaceutical companies future products would consequently suffer.

The existence of competing DCBs with no central approval agency would have a large depressing effect on the costs of R&D required for the introduction of a new drug. Unnecessarily stringent rules and procedures for clinical tests, dictated by overly cautious central agencies, would be eliminated along with bureaucratic inefficiencies.

It is important to note that a significant decrease in R&D costs could have an especially large impact on the extensive margin. Currently, small biotech firms are finding it difficult to raise sufficient funds to survive the lengthy and costly drug development process. Fostering the entry of biotech firms into the pharmaceutical industry is important for both more innovation and competition with traditional pharmaceutical firms. In the U.S, 30% of all drug approvals in 2002 went to biotech drugs.¹¹ In 1999, they only represented 6%. According to the European Commission, half of the new medicine in development today is based on biotechnology. A less costly drug approval process would not only lower the costs and prices of NCEs but it would also bring more players into the biotech market leading to even more innovation, competition and cheaper drugs.

The increased entry of small biotech firms into the market could offset the waning of the generic industry in the scenario of a competitive market in drug approval that did not compromise intellectual property rights through violations of data protection. In any case, fierce competition among brand names already exists in the industry. Lack of competition or concentration is not the reason for high drug prices. DiMasi (2000) shows that for new drugs that are substitutable with existing drugs, the opening market price is very often lower. Out of 20 drugs examined during the 1995 to 1999 period, 13 of them were launched at a lower price than the existing drug, and five were introduced at the same price.

A competitive market in DCBs would completely eliminate an economic justification for violating intellectual property rights. Once the cost of developing medicine and its price were sufficiently reduced, the data generated by innovators in clinical trials could safely become unrestricted private property. Another benefit would be that there would no longer be a need

for legislating and re-legislating complicated data exclusivity laws.

It should be mentioned that there are other arguments, non-economic in nature, in favor of compromising data protection. One argument rests on the consumer's right to know the test results. Ollila and Hamminki (1996) make a case for more transparency in this regard. The existence of DCBs would not totally resolve this problem, but consumers would at least have the right to choose which DCB to trust, and arguably have more indirect knowledge of the reliability of a DCBs tests than under a centralized regulatory system. The profitability of the DCB would serve as a strong signal of the reliability of their approvals.

Another non-economic argument against data exclusivity is that it leads to the needless replication of testing, especially on animals (see Dukes (1996)). However, technological advancements may render animal testing obsolete in the near future. Xgene Corporation is pioneering a novel skin development technology that will enable pharmaceutical compounds to be tested on skin instead of animals. The pharmaceutical industry is also aware of the ethical issue of using animals in pre-clinical trials. In the UK alone, \$477 million per year is spent on developing new technology that could replace the need to do animal-trials.

Conclusion

Obtaining drugs at lower prices is a priority public policy issue. Ensuring continued pharmaceutical innovation is also critical for increases in longevity, better health, higher productivity and economic growth. Balancing the price of medicine against incentives for continued drug innovation is a difficult challenge facing legislators.

This paper argues that drugs are expensive not because of a lack of competition among research-based pharmaceutical companies, but because of a lack of competition in the drug approval process. Permitting the violation of intellectual property rights through weak data protection laws and easy entry for generic products is not the correct solution to the drug price problem. Artificially low prices combined with exceedingly high and ever-increasing drug development costs will lead to

substantially lower levels of pharmaceutical R&D and innovation.

A better solution to the drug price problem is to reform the regulatory drug approval process through privatization and competition. The replacement of national drug administrations with competing drug certification boards, with the power of final approval, would decrease the costs of drug development without compromising public health. It would lead to lower drug prices and preserve the incentive to innovate.

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Notes

1 R&D investment by pharmaceutical companies amounted to more than \$60 billion in 2003 in the U.S and in Europe. The Association of the Pharmaceutical Research and Manufacturers of America (PhRMA) reported an estimated \$33.2 billion on R&D expenditures in 2003, The European Federation of Pharmaceutical Industries and Associations (EFPIA) reported R&D investment of 21.1 billion euros for the same year.

2 Levin et. al (1987) argue that, in general, firms that produce easily copyable goods, like pharmaceuticals, chemicals, and software are generally more concerned with IPRs than firms investing in products that are costly or difficult to imitate, like computer hardware or electronic assembly equipment.

3 According to calculations by Murphy and Topel (2002), if medical research were to find a cure for cancer it would be worth \$47 trillion in economic value. Griliches (1992) argues that R&D, in general, is the most important factor explaining the growth of per capita income and consumer welfare during the 20th century.

4 See IMS http://www.ims-global.com//insight/news_story/0111/news_story_011106.htm

5 Belgium, France, Germany, Italy, The Netherlands, Sweden and the United Kingdom have a ten year limit. Austria, Denmark, Finland, Ireland and Luxemburg have a six years limit. Greece, Spain and Portugal have a 6-year limit or until expiration of the patent, whichever comes first.

6 Abrantes-Metz, R., Adams, C. and Metz A. "Pharmaceutical Development Phases: A Duration Analysis," Federal Trade Commission, Working Paper # 274.

7 Because of their novelty, fewer studies on duration and probability of success have been conducted for biological drugs. Biological drugs first appeared in the market in 1984, and by 1994, only 29 biological entities were marketed in the U.S.

8 As a consequence, the Medicines Control Agency (MCA) was able to raise half of its income from fees charged to the pharmaceutical industry.

9 Note that AIDS groups are now lobbying for a relaxation of drug approval requirements. See for example the Gay Men's Health Crisis (GMHC) at <http://www.aegis.com/pubs/gmhc/1996/GM100503.html>

10 Many big food companies demand certification from KCBs with the highest standards in order to appeal to the largest number of potential consumers.

11 This figure includes monoclonal antibody and recombinant protein products. (SMD,rDNA and mAb therapeutics).

Reducing Barriers to the Development of High Quality, Low Cost Medicines: A Proposal for Reforming the Drug Approval Process

The current drug approval process is slow and costly. Moreover, the disclosure of confidential data to national regulators, and the subsequent use of this data to support regulatory approvals by competitors, diminishes the incentive to innovate. As a result, many potentially life-saving medicines are not developed and the delivery of many more is unnecessarily delayed.

Activists complain that too few drugs are developed and the prices charged for medicines excessive. Governments have typically used a heavy-handed approach to such complaints, employing a combination of price controls on medicines and public subsidies to drug development. However, these policies do not address the underlying problem – indeed, they tend to exacerbate it.

One solution to address part of the underlying problem would be to enhance competition in the regulation of pharmaceuticals. The authors argue that ideally this would happen through the privatization of existing regulators, and open competition between private certification boards. Such privatised regulators would set the standards of regulation at levels demanded by those making choices about drug regimens. For many drugs, this would mean swifter approvals and a reduction in development costs, leading to an increase in the number of drugs developed for most diseases – especially those which affect the poorest and those which affect smaller populations – while also reducing the price of medicines to all.

In addition, under a privatised regulatory system it is likely that different certification boards would target different groups. For example, some might focus on the implications of drugs for specific populations, such as the elderly or children, while others might focus more on long-term effects. As a result, doctors and consumers would be able to make more informed choices about drug regimens.

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