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The dynamics of knowledge accumulation, regulation, and appropriability in the pharmaceutical sector: policy issues

LUIGI ORSENIGO, GIOVANNI DOSI,
AND MARIANA MAZZUCATO

THE contributions to this book enrich from a variety of angles our understanding of how the dynamics of knowledge affect the dynamics of firms and industry structures. In this concluding chapter, we discuss some associated policy implications regarding the future of the innovation process in the pharmaceutical industry and the institutional setup supporting it.

14.1 Institutions, industry organization, and innovation: a bird's-eye view

The policy debate in this arena has become extremely intense and often bitter in recent years. The issues at stake concern an area – health care – the importance of which for society is fundamental and rapidly increasing; indeed, they are becoming crucial elements in the very definition of notions such as welfare, justice, and democracy in the new century.

Many fundamental issues in the policy debate on the pharmaceutical industry, however, are certainly not new. Ever since its inception the market for drugs has been (almost) always and everywhere regulated, albeit for different reasons and in different ways. At the same time, the extent and the forms of the regulation have most often sparked discussion and conflict. For example, considerations linked to consumer protection led, throughout most of the twentieth century, to increasingly stringent requirements for the approval of new drugs, and implied larger and more costly clinical trials. The presence of significant information asymmetries in the market for drugs coupled with fundamental considerations of social and economic equity have often been used to justify the introduction of various forms of price regulation. The emergence of the welfare state and the subsequent rise of health care and prescription drug spending have induced, first, a rapid expansion of

demand, and then a series of cost containment policies. Developments in legislation and in courts' interpretations of issues concerning intellectual property rights have also had significant impacts on patterns of competition and industrial evolution. Last, but certainly not least, the institutional setups governing the systems of fundamental scientific research have profoundly affected the ability to discover, develop, and commercialize new drugs.

More broadly, it is important to recognize that policies and institutional design have deeply affected innovation and industry evolution, sometimes consciously, sometimes through the unintended effects of interventions taken for reasons by and large independent of considerations related to the performance of the industry. These interventions and the evolving institutional structures have influenced the patterns of accumulation of competencies, the selection mechanisms, and the incentive structures to engage in innovative activities in many different, and sometimes indirect, ways.

Policies have also evolved. Certainly, they often display inertial elements, embedded in and shaped by specific institutional and political environments. However, institutions and policies have been profoundly influenced by technological change – especially at times marked by profound technological discontinuities. And they are also deeply influenced by changes in the broader “political economy” of any one country and the ideological orientation of each historical period. For example, major technological and scientific breakthroughs, such as the “antibiotic revolution” in the 1930s and the emergence of biotechnology in the 1980s, have substantially changed both non-market institutions and industry dynamics. The possibility of discovering and developing new drugs was (and is) not just an occasion for firms to make profit. It has also changed the procedures, forms of organization, and costs of research, as well as the attitudes of people towards health care.

Together, the boundaries between the activities that ought to be regulated explicitly by the public authorities or even undertaken by them directly versus those left in the hand of profit-seeking entities happen to be deeply influenced by the prevailing *Zeitgeist* on the virtues and shortcomings of market processes, as compared to political decision processes. Indeed, the definition of health care itself – and of people's medical needs – depends both on the status of scientific and technological progress and, together, on fundamental social visions on

the very meaning of *citizenship* and *rights*. For example, does every citizen have the “right” to some form of “care”? And, if so, up to what limit? (We return to this question of *rights* in the final section of the chapter.)

In short, technological change has been and remains dynamically coupled with institutional and political change (more on this in Lacetera and Orsenigo, 2002).

The “golden age” of the pharmaceutical industry (from the end of World War II to the 1980s) was supported by a few interrelated factors. The explosion of public support for health-related research provided ample technological opportunities to be exploited. Firms developed highly effective organizational procedures for discovering, developing, and marketing drugs, refining the so-called a “random screening” paradigm. The international oligopolistic core of the industry, which is now called “big pharma,” came to dominate under such a learning regime. Growing incomes sustained a fast-growing demand, which – especially in “welfare states” characterized by national health care systems (most of them in Europe) – offered a rich, “organized,” and publicly regulated market for drugs.

Recently, however, this picture has been drastically transformed. As discussed in several chapters of this book, the industry has experienced a number of interrelated transformations in recent years.

The “molecular biology” revolution has fostered the emergence of a new technological paradigm, potentially involving immense new opportunities for innovation – which, however, have only very partially materialized so far. If anything, the costs of research have been soaring, many analysts claim partly as a consequence of tighter procedures for product approval (this is indeed a matter of controversy, which we shall touch on again below). Meanwhile, the crisis of the welfare state – and, more generally, the explosion of public expenditure for health – has fueled attempts to reduce public outlays in this domain.

The spreading of attitudes and legislation in favor of a tighter intellectual property regime (the Bayh–Dole Act in the United States and international TRIPS [Trade-Related aspects of Intellectual Property Rights] agreements being the sharpest examples), not least in areas traditionally characterized by more lenient appropriability conditions (including, of course, freely accessible publicly funded scientific research), has radically changed the conditions with which knowledge is created, diffused, and accessed.

Newly industrializing countries – such as India and Brazil – have meanwhile emerged as potentially important players in the world pharmaceutical industry, mainly but not exclusively as producers of generics for other developing countries. As a result, the very viability of the business model that dominated the industry in the “golden age” has been called into question. At the same time, the demand for health care and the expectations of the population are continuously rising, and the many humanitarian catastrophes in developing countries highlight the paramount importance of access to drugs by the world’s poor.

As already briefly mentioned in the introduction to this book, policy prescriptions crucially depend on a few, very difficult, interpretative issues, including:

- the impact of different patent systems upon (i) the *rates* and directions of innovation, and (ii) their ultimate *distributive* and *welfare effects*;
- the trade-offs and dilemmas between the increasing costs of drugs and health care in general, together with the need to contain public expenditure in this field, versus the demand for (or “right” of) access to drugs by the whole population in rich (and aging) countries, and increasingly so in the poorer countries as well.

The price of drugs is, clearly, one of the crucial issues (albeit not the only one) at stake. To what extent are free (high) prices necessary to sustain innovative activities and the viability of the industry? And how can high prices be reconciled with the need to make drugs accessible to the widest possible share of the population and with the budget constraints of the various states?

It is worth remembering that, perhaps in different forms, these questions have been there throughout most of the history of the industry. The debate around the Kefauver Commission of the US Senate, which around half a century ago investigated monopolistic positions in the American industry, addressed many of these issues, in fact. Nonetheless, the following three issues introduce some elements of genuine novelty into the debate.

- (i) The growing and more direct role of scientific knowledge in the process of innovation in the pharmaceutical industry, as a consequence of the “molecular biology revolution.” This role is particularly evident in drug discovery, but science is increasingly relevant also in drug development, in the processes of product approval, and in the evaluation of the post-marketing performances of drugs.

- (ii) The question marks concerning the very sustainability in the long run of the current structure of the system of innovation and health care provision, which simultaneously faces higher costs, higher expectations, and tighter budget constraints.
- (iii) The role of developing countries, both as producers of drugs and as consumers in desperate need, confronted by the challenge of increasingly difficult access to proprietary drugs.

In what follows, we briefly comment upon some of these crucial issues. First, we touch upon the question of price and other forms of regulation. Then, we move to IPR, in particular with regard to patents and the exploitation of basic, publicly funded research in general and developing countries in particular.

14.2 “Market failures” in the pharmaceutical industry

The market for drugs, as mentioned above, has been (almost) always regulated, for a variety of different reasons that may easily be accounted for both in the standard economic framework as well as in more heterodox ones. Many of these reasons can be straightforwardly explained on the grounds of the standard economic tools, in terms of market failures and standard economic efficiency.¹

The market for drugs is inherently characterized by information asymmetry. Producers inevitably have “more information” on the quality of drugs than consumers do. Moreover, it is the prescribing doctor who makes the decision, but even doctors often do not know in detail the properties of a drug, especially when it is a new one. As a result, there are a number of arguments in favor of regulation.

- (i) It is observed that much of the information available to physicians is provided by the companies themselves. As a consequence, an external assessment of the safety of the drug (and in many places, starting from the early 1960s, of its efficacy) may be necessary to prevent damage to consumers.
- (ii) Given the value that users may attribute to the product, especially in extreme cases, demand elasticity tends to be very low – even within the same class of therapeutical products (and, of course, it is zero across them: no one with a kidney problem would accept a

¹ See also Comanor (1986), Scherer (2000), and Schweitzer and Comanor (2000) for reviews of these issues.

drug for headache simply because it is cheaper!). Furthermore, most consumers are insured (privately or publicly) against at least a part of the cost of prescription drugs, so they are only marginally interested in drug prices. Similarly, the prescribing physicians are not completely sensitive to prices, both because they will not pay for the prescribed drugs and because the respect of professional norms makes them more attentive to the safety and therapeutic value of medicines. Despite their role of scientific experts, however, physicians' prescribing behaviors do not seem immune to other forces, such as advertising and brand loyalty, and seem to follow routinized patterns. (All this, of course, is premised on the assumption that there are no corrupting linkages between drug producers and prescribing doctors.)

- (iii) A related set of reasons for regulation refers to cost containment. In countries with a national health service or where there is a third payer (typically, an insurer), demand elasticity to price tends to be lower than would otherwise have been the case. This may lead to price increases by firms enjoying market power. Moreover, as a consequence, the absence of any countervailing measure is likely to lead to an explosion of public expenditures, because neither the patients nor the physicians ultimately pay for the drugs. Thus, governments may appropriately act as monopsonist and, through various instruments, try to reduce (quasi-monopolistic) profits and the maximization of drug prices.

In fact, on the supply side, the pharmaceutical industry is inherently characterized by non-price competition. Many chapters in this book elaborate on the notion that innovation is a major form of competition in this industry. In turn, producers are attributed (temporary) monopoly power through patent protection. In the absence of such protection, profit-seeking firms – the argument goes – would not invest in research or would underinvest as compared to the “social optimum” (whatever that may mean). Indeed, pharmaceuticals is one of the few industries in which patents are considered very important mechanisms of appropriability for the economic outcomes of innovation. Given the existence of (even temporary) monopoly power, (price) regulation might therefore be justified as a mechanism to counteract monopolistic pricing.

- (iv) The pharmaceutical industry is a science-based sector, wherein scientific knowledge plays a central role and is only in part

appropriate. Part of the knowledge that is used to produce new drugs is generated by and/or based on publicly funded scientific research, in principle available to everybody through publication. Thus, pharmaceutical companies are at least partly “subsidized” through publicly funded research.

- (v) Advertising, wherever it is allowed, might powerfully interact with market power. Most obviously, it might just be misleading. In any case, it tends to generate brand loyalty effects and therefore some positive feedback on profitabilities, which may have little to do with innovation and the intrinsic properties of the various drugs. In turn, both R&D expenditures and advertising involve high fixed, sunk costs, which happen to be powerful mechanisms sustaining oligopolistic/monopolistic positions and, together, provide ample opportunities to exploit them through “excessive” prices (which for our purposes here may be defined as prices in excess of those that would have justified the search investment for the new drug in the first place).²
- (vi) Even more importantly, a fundamental argument in favor of regulation is based on equity and moral considerations, and makes, to a large extent, the analysis of market processes a social rather than a purely economic issue. Shouldn’t everybody have access to drugs, including (new) expensive ones? Regardless of the different attitudes (across time and countries) towards the industry and its regulation, the main goal of state intervention has often been to guarantee the access to safe and (later on) efficacious drugs to the largest possible share of the population (certainly in Europe, but to some extent also in the United States).

The policy-maker thus faces different and possibly contrasting objectives: in brief, the goal of efficacious and safe drugs, and of equity in their availability to the population, has to match the economic incentives to induce investment in research on new medicines by profit-seeking actors in so far as the latter undertake uncertain search, testing, etc.

To sum up, the question is not so much whether to regulate or not but, rather, *what kind of regulation?*

² Of course, this takes into account the rates of investment in all would-be drugs, most of which turn out to be failures.

14.3 Price controls and product approval regulations

During the “golden age” the pharmaceutical industry was subject to rather tight forms of regulation in most countries concerning prices and the procedures for product approval. Different forms of price controls were adopted in most industrialized countries, the United States and Germany being two major noteworthy exceptions. Conversely, it was the United States that introduced the first severe and strict regulations for product approval with the 1962 amendments.³ Other countries (primarily the United Kingdom) followed, but the American procedures have remained among the toughest for a long time.

Since the late 1970s, however, two contrasting tendencies can be observed. On the one hand, price regulation has increasingly been considered an inefficient mechanism to protect consumers: the argument here is that not only do they obviously generate hostility in the industry, they also supposedly stifle innovation and introduce distortions in the market. On the other hand, the increasing need to contain public expenditures on drugs has fostered the introduction of drastic cost-cutting measures. The result has been a general move (quite heterogeneous across countries) towards the adoption of more sophisticated and less invasive measures of price control, such as policies aiming at intervening on the demand side of the market to make patients and health providers more cost-conscious and more price-sensitive (e.g. various forms of co-payment, and other interventions attempting to change the behavior of providers through financial incentives and penalties), and the development of the market for generics and systems of cost sharing such as “reference pricing.” However, in some countries, notably the United States (somewhat ironically), the arguments in favor of stronger regulation of the price of drugs are increasingly being voiced at the center of the political debate. (Of course, stronger regulation remains both harmful and unacceptable whenever undertaken elsewhere – but this is another story.)

³ The Kefauver–Harris Amendment Act of 1962 introduced a proof-of-efficacy requirement for the approval of new drugs (based on “adequate and well-controlled trials”) and established regulatory controls over the clinical (human) testing of new drug candidates. As a result of these amendments, the FDA went from being simply an evaluator of evidence and research at the end of the R&D process to an active participant in the process itself (Grabowski and Vernon, 1983).

The evidence concerning the impact of procedures for product approval and price controls on innovativeness is ambiguous, however. While the 1962 amendments in the United States and the related introduction of tougher requirements for drug approval certainly caused substantial increases in drug development costs, it is much less well established empirically whether they were responsible for lower rates of innovation. Indeed, Thomas (1994) has quite convincingly argued that a less lenient regulatory environment contributed to the take-off of the British pharmaceutical industry as compared to the French one, by conferring an advantage on more innovative firms and penalizing “me too” producers.

The evidence on price controls is far from clear. Several scholars have suggested that in the United States, lacking price regulations, higher profits have led to higher investment in R&D. Symmetrically, along the same line of interpretation, many have suggested that “invasive” command- and control-oriented approaches are likely to generate hostility between regulators and companies, resistance to change, and a low propensity to innovate. Japan, Italy, and France are quoted as examples where the imposition of tough price control mechanisms appears to have introduced strong disincentives to undertake innovative strategies and favored the survival of inefficient companies, undertaking little R&D or none at all and only marginally improving on existing products (often exploiting the absence of product patent protection). However, the British system of price controls, introduced in the 1960s, does not seem to have unduly discouraged innovative activities – possibly the opposite (Thomas, 1994). And even an industry such as the Italian one emerged as a significant innovator in a period of price controls and a lack of patent protection and nearly disappeared under a more *laissez-faire* regime.

The bottom line, at the very least, is that there seems to be no simple and unambiguous (let alone monotonic) relation between any single aspect of regulation (e.g. free versus controlled prices, the toughness of the product approval procedures, different systems of inducing cost constraints, etc.) and the degree of innovativeness – even abstracting from more demanding measures of collective performance that take into account justice and equity.

Perhaps it might be more useful to think in terms of “systems of institutional governance” rather than isolated policies. Specific combinations of different forms of regulation and competition have, in the

past, managed to produce particular competitive environments favoring both the adoption of successful innovative strategies and their fruitful social use.

Moreover, it is worth noting that many of these institutional arrangements were not devised with the explicit aim of supporting innovation, or even industrial prowess. Rather, they resulted from different purposes – such as social policies or science policies – but ended up bearing important consequences for the capacity and willingness to innovate, sometimes after quite prolonged periods of time.

In sum, the evolution of regulatory regimes has interacted throughout the whole history of the industry with the changes in the nature of technological regimes and with the social perceptions of what is considered efficient, just, and fair. It often did so, to repeat, in rather unintended ways, as the outcome of differentiated and sometimes seemingly unrelated small-scale acts of intervention in various domains, more often than not enacted by different agencies for different purposes (e.g. the Department of Health, the Treasury, the Department of Industry and Trade, etc.). In fact, one of the few robust features of the industry is indeed the profound embeddedness of its evolution in the institutions governing the non-profit-motivated generation of knowledge, on the one hand, and those concerned with the public access to health care, on the other.

Given that, what does the evidence suggest on the *technological and social* outcome of different regimes for the private appropriation of technological knowledge?

14.4 The role of patents and recent changes in patenting behavior

It is empirically well established that in pharmaceuticals – differently from several other sectors – patents are a fundamental instrument for protecting innovation from imitators. To recall, patents have a dual role in the innovation process. On the one hand, they are meant to stimulate innovation by guaranteeing the ability of innovating firms to appropriate the rewards/profits by shielding them from imitation. On the other hand, by forcing the patentholder to codify all the relevant information regarding the new (often tacit) knowledge and to make it public, they are meant to foster the eventual diffusion of the knowledge (which could otherwise remain secret) and its actual application in the commercial domain.

The possible welfare gains and losses associated with patents have been discussed extensively in the economic literature.⁴ Indeed, the links between patent protection and innovative performance look less direct than is usually assumed. In general, the empirical evidence regarding the relationships between the tightness of the patent regime and the rate of innovation is surprisingly thin. Even abstracting from the intricacies of the theoretical debate, it is worth reminding ourselves that patent laws involve many different aspects and subtleties (e.g. the scope of patents, the costs of litigation and the enforceability of IPR, the rules governing the definition of priority, etc.) that are likely to have fundamental consequences for the actual degree and form of protection for innovators. Furthermore, changes in the degree and in the forms of protection from imitation for innovators are unlikely to have monotonic effects on innovative efforts or, even more so, on the rates of innovation. Putting it more bluntly, there is virtually no robust evidence supporting the idea that higher expected profits translate into higher search efforts and more frequent innovative successes. Of course, if the expected profits are zero, most often search investments by private agents are zero too (but not always: see the open-source software story!). In any case, above some appropriability threshold incentives do not seem to exert any major impact upon the rates of innovation. Rather, the latter seem to be critically affected by the nature of paradigm-specific technological opportunities, the characteristics of the search space, and the capabilities of would-be inventors.

In order to illustrate this point naively, note first that strong innovating companies, active throughout the world, have historically used instruments other than patents to extract profits from their innovations, even in countries where patent protection was low. For example, advertising, direct foreign investment, and licensing have performed as powerful mechanisms for appropriability, especially in an era when generic competition was not as strong as it is today.

Second, the organizational capabilities themselves developed by the larger pharmaceutical firms have acted as a mechanism of appropriability. Consider, for example, the process of random screening (discussed at length in chapter 8) – i.e. the fundamental procedure

⁴ Two of us discuss at greater length the issue of *appropriability* in Dosi, Orsenigo, and Sylos Labini (2005), where the reader can also find the background references.

governing drug discovery in the era after World War II. As an organizational process, random screening was anything but random. Over time, major incumbents developed highly sophisticated processes for carrying out mass screening programs, which required systematic search strategies as well as the relatively rigorous handling of large amounts of data. Since random screening capabilities were based on organizational processes and tacit skills internal to the firm, they were difficult for potential entrants to imitate, and thus they became a source of first-mover advantages. In addition, under the random screening paradigm, spillovers of knowledge between firms were relatively small, so incumbents having a pre-existing advantage could maintain it over time with respect to firms wishing to enter. Moreover, incumbents relied on the law of large numbers: relatively little could be learned from the competition, but much could be learned from large-scale screening in-house. Each firm needed access to the appropriate information infrastructure for its therapeutic areas (Henderson, Orsenigo, and Pisano, 1999; Pisano, 1996), and that tended to reproduce the advantage of incumbency.

Third, the scope and efficacy of patent protection in pharmaceuticals has varied significantly across countries and over time. Murmann's (2003) comparisons of the role and effects of patent laws in the United Kingdom and in Germany on the emerging synthetic dye industry is quite revealing in this respect. The UK legislation allowed product patents, whereas Germany had no unified patent law until 1877. The Patent Law of that year instituted a rigorous examination by the Patent Office before a patent would be granted, in order to define precisely the scope of the claim. The rigor of the examination process – much tougher compared to that in the United States and, especially, the United Kingdom, at least until 1905 – made a patent legally much more secure once it was granted, by reducing the risk of litigation. In turn, this facilitated the creation of a market for patents, whereas in the United Kingdom patents were often the object of intensive, uncertain, and costly litigation. The German law, however, allowed only *process* patents and required that they be actually applied within the country, whereas this was not the case in the United States and – in practice – in the United Kingdom. As Murmann argues, these features of the patent system were very important in establishing the German dominance in chemicals and in pharmaceuticals. The legal grant of strong *product* patents early on in the history of the British and French industries

prevented the entry of new firms and gave few companies monopoly profits without their being forced to develop strong competitive capabilities. Moreover, frequent and costly litigation over patents among British firms further weakened both their ability and the economic interest to search for new products. Conversely, the German system allowed the industry – not simply individual monopolists – to grow and to construct such capabilities, also exploiting the ample possibilities of infringing British patents. As the German industry established itself as the world leader in chemicals, the domestic patent regime began to act as a reinforcing mechanism, providing further incentives to innovate – especially as it concerned processes – and to build systematic R&D efforts. The absence of product patent protection at home, in fact, promoted not only the diffusion of but also, less intuitively, *trade* in knowledge, contributing to the formation of an early (formal and informal) market for technology.

It is worth noting that, while the United States has always provided relatively strong patent protection in pharmaceuticals, many other European countries did *not* offer protection for pharmaceutical *products*; as in Germany, only process technologies could be patented. France introduced product patents in 1960, Germany in 1968, Switzerland in 1977, and Italy and Sweden in 1978 (and Japan in 1976).

More recent experiences of changes in IPR regimes raise further questions about the actual effectiveness of stronger or weaker patent protection on innovativeness and industrial growth.

The United States and Japan represent two important cases where patent legislation has been strengthened. In the United States, over the past twenty years, extremely aggressive institutional changes in the IPR system have been introduced. These reforms, taken together, involved cost and time reductions in patent applications and evaluation; the extension of patent duration for some classes of products (primarily chemical and pharmaceutical technological classes); and encouragement for non-profit research institutions to patent and market technologies developed through public funding. The Bayh–Dole Act of 1980 clearly falls into this latter category. Also, in Japan, a 1988 reform introduced significant changes in patent laws, implying broader patent scope coupled with an extension of the protection period for pharmaceutical products. In both cases, however, the evidence does not seem to support unambiguously the hypothesis that a tighter IPR regime automatically leads to an increase in innovative activities.

In the case of the United States, Mowery et al. (2001) have shown that the emergence of the “industry–university complex” (Kenney, 1986) and of the “entrepreneurial university” well pre-dates Bayh–Dole, while depending critically on the rise of the two main technological revolutions of the second half of the twentieth century, namely microelectronics and, more so, biotechnology. Moreover, Mowery et al. (2001) emphasize that much of the university patenting activity observed after the Bayh–Dole Act stems from long-standing characteristics – in terms of scale and structure – of the US academic system. In a somewhat different vein, Kortum and Lerner (1997) have investigated the reasons for the observed massive increase in the number of patents that has occurred in the United States in the preceding ten years. Their results seem to support the so called *fertile technology hypothesis* – i.e. that the strong increase in the number of patents is not the effect of a stronger IPR regime but, rather, a consequence of a wider set of technological opportunities, and improvements in the management of the innovative processes.

In addition, in the case of Japan, the evidence for the actual effects of reform on innovative efforts is quite mixed. In particular, Sakakibara and Branstetter (2001) show that, after 1988, there has been no substantial increase in R&D efforts. The observed rise of R&D spending actually started at the beginning of 1980 – i.e. much earlier than the year of the reform. If anything, in 1988/9 R&D expenditures showed a relative decline. Also, in the specific case of pharmaceuticals, the authors do not find any significant correlation between the increase in intellectual protection and R&D efforts.

Conversely, consider India, which is one of the few cases where there has been a weakening of IP protection: in the last twenty years, despite strong international political pressures, patent protection has actually been lowered. After these reforms, a significant *growth* in industries such as pharmaceuticals and chemicals is observed. Almost all the empirical studies on the Indian case agree that a weaker IP protection system has encouraged the development of indigenous technological capabilities and promoted catching up (see, among others, Lanjouw, 1998; Kumar, 1998, 2002).

Obviously, strong patent laws do indeed confer an advantage to innovators, but – the evidence seems to suggest – they are certainly not enough to promote innovation in contexts where innovative capabilities are low or missing altogether. On the other hand, weak patent

protection might constitute a fundamental mechanism for learning and developing domestic capabilities in laggard countries, when coupled with a complementary emphasis on pre-production research and reasonable incentive systems favoring innovative and imitative activities.

14.5 Intellectual property rights and open science

Besides the foregoing evidence (or lack of it) on the effects of IPR upon the micro-incentives to innovate, serious worries have been raised that the spread of an excessively permissive attitude towards the granting of broad claims on patents might actually slow down the processes of the diffusion and circulation of knowledge and hence the future rate of technological advance, especially as it concerns publicly funded research. More generally, several observers (e.g. Dasgupta and David, 1994; Merges and Nelson, 1990) have argued that this trend can end up seriously undermining the norms and rules of “open science.”

There is little question that science has played a crucial role in opening up new possibilities for major technological advances in biomedical research, as in most other technological fields. If anything, the role of science has been more direct and immediate in pharmaceuticals than in most other technologies. Notwithstanding the diversities across countries in the institutional systems governing the interactions between scientific and technological research (see Gambardella, 1995; Henderson, Orsenigo, and Pisano, 1999; Lacetera and Orsenigo, 2002; and McKelvey, Orsenigo, and Pammolli, 2005, for a discussion centered on biomedical research), in almost all cases (the former Soviet Union and China being notable exceptions) publicly funded science, largely undertaken in universities and in national laboratories like those of the NIH in the United States, appears to be complementary to that undertaken in private corporations. And the interactions between them have, typically, resulted in a fuzzy area at the boundaries between public and private research.

Open science has been a fundamental component of such a system, and it is responsible for the productive, yet serendipitous, two-way feedback between technological innovations and scientific knowledge. The open science (OS) paradigm (see Nelson, 2004, and David, 2004) is based on an open, accountable scientific system involving the free dissemination of results (via publications open to the public), peer review, and rewards tied to recognized contributions to the communal

scientific effort. The emphasis on serendipity – that is, the radical unpredictability of the ultimate application of any advance in scientific knowledge – also highlights, in terms of eventual technological fallout, the importance of government support for fields where practical pay-offs are less certain and direct (e.g. theoretical physics). More generally, when scientists are not constrained (by the nature of funding, and by patent dynamics) to produce knowledge that has direct and immediate practical pay-offs, the chances of this serendipity are greater (Nelson, 2004). For this reason, many students of the history of science have concluded that it is fundamental that neither the market nor the government influence too much the areas in which scientists pursue their quests for knowledge (Polanyi, 1967).

In the words of Nelson (2004):

[I]n all the fields of technology that have been studied in any detail, including those where the background science is very strong, technological advance remains an evolutionary process. Strong science makes that process more powerful, but does not reduce the great advantages of having multiple paths explored by a number of different actors. From this perspective, the fact that most of scientific knowledge is open, and available through open channels (e.g. publications), is extremely important. This enables there to be at any time a significant number of individuals and firms who possess and can use the scientific knowledge they need in order to compete intelligently in this evolutionary process. The “communitarianism” of scientific knowledge is an important factor contributing to its productivity in downstream efforts to advance technology.

In turn, as David (2004) argues, such an OS system is relatively *recent* and relatively *fragile*. It dates to the break, during the sixteenth and seventeenth centuries, from a system of knowledge pursuit dominated by secrecy and the quest for “Nature’s secrets” (e.g. the medieval and Renaissance traditions of alchemy; the medieval guilds preserving the secrets of certain trades; and mercantile secrets on trade routes, etc.). The new set of norms, incentives, and organizational structures (such as the use of peer review) reinforced scientific researchers’ commitments to the rapid disclosure of new knowledge, and to a painstaking process that developed into the research system that we experience now in the early twenty-first century.

It is, however, a delicate system, which remains “vulnerable to destabilizing and potentially damaging experiments undertaken too

casually in the pursuit of faster national economic growth or greater military security” (David, 2004), or – we would add – excessive greediness in the appropriation of the returns of the knowledge quest itself (in that, going back to the older “feudal” ethos).

Changes in patent laws and practices might constitute one glaring example of those “experiments” threatening OS. The already mentioned Bayh–Dole Act in the United States is possibly the best-known example of partly unintended consequences from the reckless manipulations of such a fragile system. To recall, the Act allowed universities and small businesses to patent discoveries emanating from NIH-sponsored research, and then grant exclusive licenses to drug companies. Along with it, a series of court cases in the mid-1990s overturned previous practices, granting patents on upstream research and significantly extending patents’ scope, even to cases in which the practical application of the objects had not been demonstrated (e.g. the BRCA1 gene discussed in chapter 11).

Many analyses (including chapters 10 and 11 in this book, and Dosi, Llerena, and Sylos-Labini, 2005) warn about the dangers of these trends. One of the problems here is that, since scientific research is usually not the final product, by strongly enforcing patents on research outputs one is potentially preventing the exploration of new outputs and products based on that research (Nelson, 2004). There are, indeed, strong reasons to conjecture that the strong enforcement (and misuse) of patent rights can stunt future innovations.

First, bringing science into the “market” is likely to distort incentives away from basic research and into specific, practical areas that promise commercial rewards.

Second, science “proceeds most effectively and cumulatively when those who do science are part of community where open publication and access to research results is the norm, and rewards are tied to recognized contributions to the communal scientific effort” (Nelson, 2004). But widening the scope of appropriability runs completely counter to this principle.

Historically, the reason for *not* granting patents on upstream research has been precisely that this could prevent the circulation of basic knowledge within the community of inventors. Similarly, granting patents on objects where the practical or commercial utility has not been proved might induce discriminatory practices that would (a) prevent the public from benefiting from the inventions and (b) prevent

future innovation (Arrow, 1962; Nelson 1959). There is little to support the idea that these reasons have ceased to apply nowadays.

Other sources of worry relate to the “anticommons problem” (Heller and Eisenberg, 1998), discussed in chapter 10, concerning the possibility that the extension of patents into research tools will limit innovation due to the *numerous property right claims to separate building blocks for some product or line of research*.

Thus, critics of the current policy trends suggest that, at the very least, one ought to enforce legally those parts of the Bayh–Dole Act that require that knowledge that emerges from publicly funded research remain in the hands of the public – one of the main points being that university research must stay in the hands of the public, regardless of whether it is patented. In fact, the Bayh–Dole Act stated that its purpose is to “ensure that inventions made by nonprofit organizations ... are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery” (Nelson, 2004). The problem is that those provisions aimed at preventing the “encumbering” are not enforced. Hence, to make sure that university contribute to the “scientific commons,” many suggest that the law must urgently be *enforced* fully and possibly reformed, to prevent, for example, exclusive and narrow licensing by universities. Unfortunately, as Nelson admits, the universities, with their new, profit-seeking goals, have become one of the main problems.

In addition to the reform of the Bayh–Dole Act, Nelson (2004) proposes to

- (i) limit the scope of patents to those that imply “substantial transformation” of the natural – as opposed to proprietary – claims stemming just from having discovered “how nature works” (on these grounds, Newton could very probably have claimed a rent on every reference to gravitation!); and
- (ii) adopt much stricter and more precise interpretations of the meaning of “utility” and “usefulness” with respect to patents (see the discussion in chapter 11).

Conversely, supporters of this “new” IPR regime argue that patents on publicly funded research serve the purpose of creating markets for knowledge. The establishment of property rights on the outcomes of research facilitates the economic exploitation of such knowledge (in the absence of patents, firms would not invest in R&D based on the new discovery because everybody could have access to it) and allows an

“ordered” path for the exploitation of such knowledge, avoiding wasteful duplication of effort. The boom in biotech companies (often founded by university scientists) is typically cited as an example of the effects of the “new” IPR regime on the commercial exploitation of basic scientific research.

Be that as it may, notice all the same that this argument is profoundly different from the standard argument, recalled above, that patents represent an incentive to innovation. In fact, this incentive is not needed in the case of publicly funded scientific research: the invention has already been paid for (by the public) and has already been realized. Moreover, the argument in favor of the imposition of property rights on otherwise open science rests on a series of specific assumptions about the mechanisms underlying the generation and economic exploitation of knowledge that – as argued by Mazzoleni and Nelson (1998) – make it very hard to accept them in general.

Clearly, these issues and their industrial policy implications are also at the core of the policy controversies regarding the institutional governance of the pharma-biotech sector. For example, what arrangements ought to govern the acquisition of knowledge by profit-seeking firms generated with public resources? What disclosure arrangements should be made? To what degree should one adjust the boundaries between what is publicly paid and universally available, on the one hand, and what is privately financed and privately appropriable, on the other?

14.6 Falling innovation rates? Fewer opportunities for innovation? Declining propensities to undertake long-term uncertain search?

The concerns over the future of the pharmaceutical industry stemming from the debates on regulation and IPR are compounded by the observation that innovation in the pharmaceutical industry actually seems to be slowing down, despite the promise of the “biotech revolution” (Angell, 2004; Nightingale and Martin, 2004; *Economist*, 2005).

Nightingale and Martin (2004) suggest that the biotechnology “revolution” has not, in fact, increased the observed productivity of R&D, because of the inability of drug firms to keep pace with the increased intrinsic complexity of the biochemical problems that innovative search is addressing. Over the period 1978–2003, research

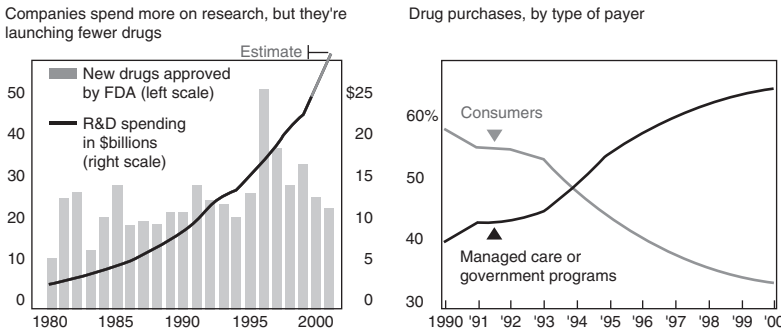


Figure 14.1. R&D expenditure, FDA drug approvals, and drug purchases, 1980–2000

Source: Harris (2002).

“productivity,” measured by the number of patents per dollar of R&D expenditure, actually fell: R&D expenditure increased tenfold, while patenting output increased only sevenfold. This is further corroborated by the number of new chemical entities (a much more demanding measure of innovativeness than patents)⁵ approved by the FDA in the United States over the period 1983–2003: some increase is recorded until the mid 1990s, followed by a sharp decline subsequently. So, in 2002, US R&D expenditures in pharmaceuticals were thirty times greater than in the early 1980s, while roughly the same number of drugs were approved annually (see figure 14.1). Considering that in recent years regulations have become more relaxed and approval times have been shortened (due to the Prescription Drug User Free Act of 1992 and the FDA Modernization Act of 1997), the fall in R&D productivity is even more surprising.

Are these patterns due to the progressive drying out of innovation *opportunities*? Arguing against this possibility, however, is the difficulty of reconciling it with the novel horizons of discovery commonly associated with the “bioengineering revolution.”

Conversely, could these patterns be the outcome of changing *directions of search* by many pharmaceutical firms, increasingly favoring

⁵ Patents are of orders of magnitude greater than NCEs because they may well concern new ways of delivering existing drugs or new combinations thereof, and, even more importantly, they include *potential* NCEs that do not achieve FDA approval because of failed efficacy tests, harmful side effects, etc.

incremental improvements on existing drug families while penalizing more uncertain long-term search? Were this the case, a challenging paradox could appear, with (i) private firms increasingly relying on non-profit institutions – *in primis*, public labs and universities – as long-term suppliers of novel basic science, while, at the same time, (ii) the same supposedly non-profit institutions are increasingly meeting incentives to undertake research projects with plausible down-the-line profitability.

Of course, there are many more sophisticated interpretations that fall between these two extremes; flagging them helps set the terms of the debate. Are we basically talking about decreasing returns to search? Is the lack of radical innovation typical of the mature phase of the industry life cycle? Is it a case of private strategic myopia? Or short-term free-riding upon past knowledge that is still untapped? Or is the growth of search/testing costs “intrinsic” to the technology-driven approach?

A complementary issue in the contemporary discussion concerns the *cost of regulation* (in part mimicking a similar debate in the 1960s and 1970s) and its impact upon the *observed* rates for the successful introduction of new products to the market (most obviously, a new drug approved by the FDA under permissive side effect rules would not be introduced under stricter ones, thus lowering the *apparent* rate of innovation).

In the multiple controversies over all these issues, Angell (2004) offers an interpretative benchmark on one side of the debate. Many economists provide the opposite view. In brief, Angell (not an economist, but a top-level practitioner in the field and a recent editor of the *New England Journal of Medicine*) makes two main suggestions.

- (i) The research reliance of the pharmaceutical industry is vastly overstated and the (corrupting) importance of its efforts on sheer market penetration are symmetrically overlooked. For example, she points out that in 1990 marketing expenditures in the US drug industry were equivalent to 36 percent of sales, compared to an 11 percent R&D allocation (subject to further caveats as to whether the “dissemination of knowledge” on a particular proprietary drug offering benefits to doctors, such as conferences located in particularly enticing environments, should be put under the “R&D” heading, as is usually the case in this industry). In this respect, note that the ratio of R&D to marketing expenditures is, in general, of no great

significance. It becomes more worrying whenever the outcomes of such marketing efforts end up being paid, directly or indirectly, by taxpayers.

- (ii) While there is little doubt that there is no relation (nor should there be) between the production costs of any particular drug and its price, Angell – along with other critics – claims that a good deal of the upfront search and innovation costs are actually borne by the public sector (e.g. in the United States by NIH-funded research).

According to Angell, big pharma concentrates on “me too” drugs (drugs almost identical to existing drugs – sometimes differing only in terms of dosage – extending the monopolistic profits of the old drug under a different name).⁶ Conversely, truly innovative drugs (i.e. new molecular entities with priority ranking under FDA procedures) almost always trace their origin back to publicly funded laboratories (either NIH labs or publicly funded universities). More than one-third of the drugs marketed by big pharma are either licensed from universities or small biotech companies. And this third comprises the most innovative element of all new marketed drugs.

Again, the issue is ultimately empirical. It would certainly be helpful if drug producers convinced of their continuing innovativeness allowed independent researchers to browse through their R&D investment portfolios and their product selection strategies.

Angell’s point can easily be rephrased in terms of the threat to open science posed by the private funding of basic research, as discussed above. Since Bayh–Dole, it is the “market,” more than open scientific priorities, that determines what type of research is pursued, and funded, in the pharmaceutical/medical/biological fields. Given the subtle synergies, complementarities, and overlappings of interests between public and private research (see Nelson, 2004), the novel, emerging institutional arrangement is likely to jeopardize not only the openness of science (discussed above) but even the technological productivity of science itself.

These criticisms are fiercely rebutted by the industry, and by many economic analysts. For example, it is pointed out that R&D intensity

⁶ The FDA allows the approval of new drugs if they are better than a placebo, not requiring the applicant to test the drug on an older, incumbent drug. In fact, many new drugs differ solely in terms of dosage, yet the millions of dollars spent on marketing make them “seem” new and better (Angell, 2004).

is, in any event, much higher than in any other R&D-intensive industry (which, under the caveats briefly listed above, is a robust fact). Given that, a possible argument in support of the continuing “progressiveness” of the industry against the unfavorable evidence regarding innovative output is in terms of the deep organizational transformation that the pharmaceutical industry is now undergoing. Following the biotechnology revolution, the role of scientific, academic, research has increased dramatically. The process by which the new – biology-based – knowledge is absorbed and adopted has been slow and painful for large established corporations (Henderson, Orsenigo, and Pisano, 1999). By the mid-1990s, however, some of them had successfully adapted, and they have again become leading innovators (Galambos and Sturchio, 1998). All in all, the structure of the industry has changed, with a stronger division of labor between the industry, on one side, and academia and the biotech companies, on the other. This phenomenon is partly due to the fact that, given the tumultuous rate of advance in biomedical research, no single organizational entity can survey and control – let alone produce – technological opportunities from relatively basic scientific advances all the way to final approved products. Moreover, as noted previously, the new IPR regime has introduced strong incentives for the creation of markets for technology and the division of labor between large companies (specializing in the development and marketing of drugs) and biotech companies (specializing in drug discovery) (Arora, Fosfuri, and Gambardella, 2001).⁷ And the slowdown in innovation could result, as suggested by Nightingale and Martin (2004), from the difficulties and the time lags involved in mastering the new scientific and technological knowledge base.

This interpretation is intuitively in tune with the more general observation that new technological paradigms take time to establish themselves, and their diffusion into the economy requires concomitant changes in the whole organizational and institutional structure of the economy (Freeman, 1995; David, 1990). In the case of pharmaceuticals,

⁷ It has to be noted, however, that, while the tendency towards the division of labour is certainly undeniable and very strong, specialization is far from complete, especially as far as large corporations are concerned. For example, interactions between big companies and biotech firms do not occur solely and simply via market-mediated transactions in which the latter sell a discovery to the former. Rather, a large fraction of these interactions take place at the preclinical stage. See, for example, Orsenigo, Pammolli, and Riccaboni (2001).

it may well be that new products are still in the phase of infancy with respect to their full potential uses throughout the economy (agriculture, medicine, life science research, etc.) – as happened with electricity, cars, and the PC, when it took almost thirty years for the new product to be adopted by mainstream businesses and consumers (Wong, 2005).

Clearly, the foregoing alternative scenarios depend critically on whether, and how, the biotechnology revolution will deliver its promises. But in all cases the question remains open as to whether the traditional business model as incarnated in big pharma is still viable, and/or what the functions are that it might perform. Can big pharma companies continue to be crucial agents in the innovative process, along – and interacting – with academia and biotech companies? Will they perform the function of integrators of the different fragments of knowledge and capabilities that are required to produce a new drug? Or, as the division of innovative labor deepens, will they progressively lose their innovative capacities, and even their “absorptive capacities” – i.e. the ability to understand, evaluate, and absorb new, externally created knowledge? Will the large established pharmaceutical companies become (or, as Angell suggests, remain) essentially marketing-based organizations, the function of which is “simply” to conduct clinical trials, get approval for the products, and sell them?

Yet another interpretation is the view that, in fact, biotechnology is not a “revolution” by any means, but, rather, that (as suggested by Nightingale and Martin, 2004) the stagnation, or even fall, in innovative output is the outcome of an incumbent “maturity” of the industry characterized by a *fall* in innovative *opportunities* – a little like the mature phase in the life cycle of such industries as steel or automobiles (Klepper and Simons, 1997).

As yet there are no clear-cut answers to these questions. Whatever the answers are, though, they bear fundamental implications in terms of policies.

14.7 Some provocative policy issues by way of a conclusion

First, note that a good deal of the debate on patents and the regulation of drug prices boils down, from a normative point of view, to the relationships (a) between the (actual and expected) profitabilities and rates of investments in innovative search and (b) between the latter and actual rates of discovery.

Concerning point (a), to our knowledge there is no clear evidence either way. The (cross-sectional) evidence on different firms simply confirms their different propensities to undertake R&D – that is, different innovation/imitation strategies amongst firms. Conversely, over time, the observational windows are too short to infer anything whatsoever about the strategic reactions of various firms to changes in appropriability regimes and profitabilities (while, of course, self-serving claims should not be taken too seriously).

Concerning point (b), let us just remark that one cannot claim *at one and the same time* that the industry invests a great deal in truly innovative search, that opportunities for innovation have increased due to the biotech revolution, and that the rates of successful innovation have actually remained stagnant or fallen (unless one claims, as is often done by big pharma, that *increasing* testing requirements and *increasingly* stringent selection criteria based on safety grounds are the major cause of the observed patterns – which is, frankly, a far-fetched claim, given that in recent years regulations have become more relaxed and approval times have been shortened, as a result, for example, of the Prescription Drug User Free Act of 1992 and the FDA Modernization Act of 1997).

Clearly, the outcome of such controversies entails big economic stakes. For example, if much of the search and preclinical test discovery occurs “upstream,” within non-profit, publicly funded institutions, the argument in favor of OS institutional arrangements is tremendously strengthened. Conversely, if large corporations become specialized in product development, approval, and marketing, one reasonable scenario would be for non-profit, mostly public, agencies to move downstream one step further into clinical trials. What would the economic arguments be for and against having pharmaceutical companies mainly *producing and distributing* drugs, as they already largely do in the case of vaccines, on (quasi-)marginal cost rules? Why not have the whole range of search/development/screening/testing activities in the hands of non-profit organizations or ad hoc subcontractors thereof, given that the public, one way or another, pays for it in any case?

Second, let us end with an even broader and more provocative suggestion, concerning the very notion of “universal rights” for decent health care. In this respect, the notion of “market failures” misses, perhaps, a fundamental dimension of the problem. Should public

support for scientific research be justified (or criticized) only in terms of a market outcome? And is therapeutical knowledge only a “public good” – i.e. non-rival in nature and freely accessible at zero cost? In all probability, most would consider health to be a value in itself, for individuals and for society as a whole, at least at a “minimum and decent” level. If so, what should that level be, in so far as it is constantly redefined by the interaction between technological opportunities, expectations, and perceptions of what is right and wrong, as well as its costs? Consider an extreme but revealing example. Should one define the access to drugs and treatment for HIV/AIDS by people in Africa as a public good? This sounds genuinely awkward. Many of us would rather consider it a basic human right.

In economics, the concept of human rights looks much like an oxymoron: something that is (should be) priceless, but costly. The “economics of human rights” is a vast and unexplored field of analysis. However, in all likelihood, it is going to be quite different from the standard analysis of public goods. A good starting point might be the observation that “goods” such as education, defense, environmental preservation, etc. should be funded and supported by the state because of their sheer importance to the social fabric and government’s responsibility towards its citizens – i.e. societal “values” as to what is right or wrong, justice, fairness, etc. – rather than the state’s role simply being one of fixing “market failures” (Nelson, 2004).

There are sound reasons to believe that science and the preservation of an “open” and accountable scientific system, based on the widespread dissemination of results, also fall into the category of universal entitlements *in their own right*, precisely because open science is grounded in values that go beyond their immediate practical and economic function, and is part of the “vital infrastructure” of society and hence the “responsibility” of society and the state.

Seen from this angle, one certainly continues to face all the economic and organizational issues insightfully addressed in many chapters of this volume concerning topics such as incentive compatibilities, organizational learning, and the strategic management of innovation. However, from a normative point of view, the division of labor between an OS system of scientific and technological discovery, on the one hand, and private profit-seeking actors, on the other, ought to be assessed under the criteria not just of economic viability but also of social “rights of access.”

Moreover, it is certainly misleading to think that “production” and “distribution” can be delinked. Pushing it to the caricatural extreme, it would be like saying that one could innocently privatize the exercise of criminal justice, with public authorities able to influence the access to fair (and expensive) producers simply by paying for private sheriffs. Rather, we are currently witnessing a period of profound institutional transformation wherein the capabilities to generate new therapeutical advances are coevolving with the distribution of their costs, the ensuing rents – all with profound effects on the very structure of the social fabric.

If this book has contributed, even if only marginally, to the understanding of such dynamics, we would consider it a significant success.

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