

INTELLECTUAL PROPERTY RIGHTS AND PHARMACEUTICALS: CHALLENGES AND OPPORTUNITIES FOR ECONOMIC RESEARCH

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1. INTRODUCTION

The pharmaceutical sector has unusual prominence in debates about IP policy, and has served as the front line for national and international controversies about the relationship between IPRs, R&D incentives, pricing and access to medicines. Notwithstanding the intensity of debate, on some crucial questions there is relatively little empirical evidence to support policy-making. This paper surveys the empirical literature on intellectual property and pharmaceuticals, discusses methodological issues and key sources of data, and identifies some of the key research issues and major gaps in the literature.

The pharmaceutical sector is complex and highly regulated in most economies. Government price controls and purchasing, public and private insurance schemes, restrictions on marketing and promotion, and the involvement of “learned intermediaries” such as physicians and pharmacists powerfully influence demand for pharmaceuticals. On the supply side, stringent product safety review, regulatory oversight of manufacturing, and legal frameworks governing technology transfer between publicly-funded biomedical research institutions and commercial entities play an equally significant role in shaping competition. Importantly, since much of the research on pharmaceuticals has been focused on questions specific to the market institutions and regulatory framework of high-income economies such as the US and the EU, the extent to which this literature provides a firm foundation for evaluating the impact on policy changes in developing countries and countries with economies in transition is therefore unclear.

IPRs are generally understood to have two principal areas of impact in pharmaceuticals. First, there is the issue of pricing and access, where discussion focuses on the links between IPRs (particularly patent rights), exclusion of competitors and the availability and pricing of new medicines. Second, there is the issue of R&D incentives – that is to say, the role of IPRs in providing incentives to discover, develop and market new drugs – and the effect of IPRs on R&D expenditure and its allocation across diseases, countries and organizations. Obviously, these two issues are closely linked, and their interplay presents a series of very difficult economic issues and policy questions.

Even in a single-country context, the use of IPRs to reach an appropriate balance between “static” gains to consumers from low prices and competitive supply of drugs with “dynamic” gains from innovative new products presents serious challenges. On the one hand, industry feels acute financial pressure from rising R&D costs and decreasing effective patent life. On the other, notwithstanding very substantial economic and health benefits associated with innovation in pharmaceuticals, even in relatively wealthy countries high prices for on-patent drugs tend to raise difficult political questions relating to equity and access for low-income or disadvantaged groups, and for setting priorities in allocating public health care budgets.

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Looking cross-nationally, differences among countries in their approaches to these fundamental policy issues present additional challenges. The supply side of the industry operates globally. Industry R&D is conducted largely by multinational companies who operate R&D facilities in multiple countries, relying on and contributing to a transnational science base, and products are sourced and manufactured globally and are sold in essentially identical form in many different countries. Yet on the demand side, markets are essentially national, with significant heterogeneity across countries in IPR regimes and health care institutions.

In principle, IPRs could support substantial (and potentially global welfare-maximizing) differential pricing across countries that reflects differences in income and in sensitivity of demand to prices. However, these price differences may create additional domestic and international controversy: for example, efforts by governments in some developed countries to lower domestic prices of on-patent drugs through price regulation or monopsony purchasing tend to be perceived by countries that pay high prices as “free riding” and it is unclear whether this is sustainable in the long run. Differential pricing also creates incentives for parallel or “gray market” trade, particularly for products such as pharmaceuticals which are easily transportable. However, if substantial arbitrage-driven trade in pharmaceuticals takes place, while prices may fall in the importing country, they will also tend to rise in the exporting country. Thus, while parallel trade may provide access to cheaper drugs in certain contexts, it may also undermine producers’ ability to charge lower prices in lower income countries and may affect their willingness to supply countries or distributors who serve as entrepôt facilities. Large volumes of arbitrage trade in legitimate products may also create additional opportunities for fraudulent or substandard production to enter the supply chain, particularly where repackaging of products or transshipping through a series of countries makes their origin difficult to determine. Counterfeiting of drugs – production of illegal copies of the products of approved manufacturers, often with misleading packaging and poor quality, incorrect, absent or impure ingredients, and as distinct from legal production of generics – is reported to be an increasing problem outside the most tightly regulated markets, though its extent is difficult to quantify.

Importantly, for any particular country, in this sector the tradeoffs inherent in IPR policy choices are highly contingent on the institutions and operation of its health care system, and the extent to which it has domestic pharmaceutical R&D or manufacturing capability. While much attention has been given to the IPR policy choices and evolving pharmaceutical markets of countries like Brazil, China, and India, and to the very difficult and very public debates about pricing and access to HIV/AIDS drugs in sub-Saharan Africa, we should be careful not to generalize from these specific cases.

The complexity of these issues demands careful empirical analysis. Yet, there are some very serious gaps in our knowledge, particularly as regards development of data that would support informative research into the impact of IPRs in this sector.

2. CRITICAL RESEARCH ISSUES

Formal welfare analysis of any policy instrument focuses on its impact on producer and consumer surplus, concepts which are well-defined in economic theory but not always straightforward to measure empirically. In this respect, the pharmaceutical sector presents some unusual challenges for assessing the impact of IPRs. Consumer surplus is particularly difficult to measure in this sector, since in many countries demand is strongly influenced by insurance schemes or government provision of drugs and “learned intermediaries”; i.e. physicians and pharmacists play an important role in consumption decisions.

Policy discussion of the impact of IPRs thus revolves around proxies for welfare, rather than direct estimates. On the supply side, these include trade and production statistics and indicators of the pace of technological change – i.e. development of new drugs. On the demand side, these include pricing and product introductions.

2.1 Characterizing IPRs

Any effort to quantify the economic impact of IPRs must recognize the complex nature of the legal framework that supports them. Subtleties in the language of statutes that create IPRs and govern their enforcement and in their interpretation by courts, administrative agencies, and other participants in the IPR system, can have major implications for the “strength” of IPRs – which are often felt quite differently across different sectors of the economy. IPRs also do not exist in a vacuum: in most countries: the legal framework of IPRs is interwoven with (and often constrained by) domestic laws and institutions governing competition policy and antitrust, international trade, labor relations, privacy and many other issues, as well as multilateral or bilateral agreements with other countries.

Consistent and comparable characterization of differences in IPRs across countries and over time is, therefore, formidably difficult. Following early efforts by Gadbow and Richards (1988) and Rapp and Rozek (1990) to develop indexes of national IPRs, a pioneering study by Ginarte and Park (1997) constructed a summary index of the strength of patent protection for 110 countries over the period 1960–90 (since updated to 2005 in Park (2008)) by coding national patent laws according to the extent of coverage of different technologies, membership in international treaties, potential to lose protection, presence of enforcement mechanisms and duration. These data have been widely used in studies of growth, development and IPRs. However, notwithstanding the very significant effort required to construct such indexes, they pose a number of problems.

First, they focus almost exclusively on patents, ignoring copyright, trademarks, and *sui generis* IPRs, and do not speak to the effectiveness of other appropriability mechanisms such as secrecy and speed to market. Further, as pointed out by Lerner (2002) in his study *150 Years of Patent Protection*, these composite ranking/rating schemes often bury important features of the patent protection regime, may obscure important sectoral differences in its operation, and do not control for complementary aspects of a country’s legal regime. Perhaps most significantly, these indexes reflect the formal *de jure* status of patent protection, rather than an assessment of the *de facto* conditions facing holders (or prospective holders) of IPRs at a particular point in time.

Pharmaceuticals are an interesting case in point. In this sector, while patents are the most visible and perhaps most important form of intellectual property, other IP instruments also play a significant role. In the product market, these include copyright in supporting publications and materials, trademark protection of brands, and administrative mechanisms or *sui generis* provisions giving proprietary rights in clinical and manufacturing data used to support regulatory approval. In the R&D domain, contract law governing license agreements, collaborative ventures, disclosure of proprietary information, as well as statutes covering the rights of inventors vs. employers and the transfer of technology by publicly funded institutions, are critical to the operation of the “market for technology”. Copyright and database protection may also be playing an increasingly important role as research relies increasingly on bio-informatics and other *in silico* research methods to analyze very large databases of genetic, clinical, and bio-physical data (Cockburn (2005)).

The scope of patent coverage in pharmaceuticals has, at least historically, been quite varied. In some countries, patent protection is available for pharmaceutical products, for production processes, for treatment protocols and dosage regimens, for the use of a drug in treating a specific disease, for packaging and delivery mechanisms, and even for metabolites of the drug produced in the body during treatment. In others, coverage is more restricted. Standards for obviousness, the level of the inventive step, and utility (or industrial application) of the claimed invention have implications for the type of drugs that are likely to be developed for a given market: very narrow scope of claims, for example, have historically promoted a proliferation of chemically very similar "me too" drugs in countries such as Japan (Aoki *et al* (2006)).

As innovation increasingly focuses on "large molecules", i.e. biotechnology, the availability of patent protection for these products, or processes for manufacturing them, has become an important issue. Many biotechnology products involve therapeutic or diagnostic use of proteins or other molecules found in nature, albeit in purified, isolated, or modified forms, or genetic modification of living organisms. While excluding such substances (or "naturally occurring processes" that create them) from patent protection may reflect well-founded public policy considerations, or efforts to lower the costs of very expensive products, these choices may affect some countries' access to such "leading edge" treatments, or reduce commercial incentives to develop these types of drugs for certain diseases or distinct patient populations.

Competitive pressure leads most pharmaceutical companies to file for patent protection on drug candidates very early in the development process, but the extraordinarily long development time for a typical product (7-10 years) leaves relatively little time to recover R&D costs through an exclusive market position. In some OECD countries, though not all, pharmaceuticals can, therefore, obtain patent-term extensions beyond the basic statutory term of 20 years to compensate for delays in the approval process. In some cases, additional periods of market exclusivity intended to promote policy goals such as development of drugs for "orphan" diseases, or testing of new drugs in children, are also available.

After the initial launch of a drug, further substantial R&D expenditures are often incurred for additional clinical testing in a wider set of indications (diseases) or patient populations, or in improving its pharmacological properties. Though such "lifecycle management strategies" are severely criticized by some observers, this type of incremental innovation may be an important source of benefits to patients. (See Berndt, Cockburn and Grepin (2006)). Availability of patent protection for new uses of existing compounds can therefore be an important consideration, though it is an open question as to whether the benefits of such incremental innovation outweigh any associated costs in any particular market.

In some countries, vigorous generic competition can be anticipated for almost all drugs. In the US, for example, under the Hatch-Waxman framework, generic manufacturers have been given strong incentives to challenge the validity or enforceability of patents (180 days of protection from subsequent generic entry if a patent is successfully challenged).

Exemptions from patent rights are available in many countries to allow testing of production processes or preparation of samples in order to satisfy regulatory requirements. However, such "Bolar" provisions do not normally extend to stockpiling of products in advance of patent expiration. Canada, for example, had an explicit provision in its Patent Act to allow this, which was found by the WTO to be in violation of Article 28.1 of the TRIPS Agreement. (Conducting independent clinical trials while a patent is still in force may or may not be covered by the "research exemption" present in the patent law of some countries.) Such rights can have a significant effect on the speed with which generics enter the market and the intensity of generic competition.

In countries where there is strong generic competition, processes for challenging/enforcing patents are critically important. From the perspective of patent holders, the ability to recover lost profits from infringers, or to obtain preliminary injunctions against alleged infringers while litigation proceeds are very important factors affecting the return on R&D. From the perspective of would-be entrants (and payers) the ability to have patents declared unenforceable or invalid, or to oppose applications for patents, or to counter-sue patent holders on the basis of violation of competition law or unfair trading practices are equally important. For both sides, the availability of timely, non-discriminatory, transparent and predictable processes for resolving patent disputes is also a material issue, as is “patent quality” – inconsistently or poorly applied standards for patentability are likely to raise the costs and uncertainty faced by all parties affected by patents.

For any product, the strength of patent protection in a country is also affected by the interaction between domestic IPRs and trade law. This is particularly important in pharmaceuticals, where transportation costs are very low relative to the value of the product, and high-quality manufacturing capacity is geographically concentrated. Provisions governing national exhaustion of IPRs, “reimportation” and parallel trade are one important area, as is the ability of patent holders to use customs procedures and trade dispute mechanisms to exclude competitors. A subsidiary trade-related issue is the extent to which a country allows “product by process” protection, namely the right to exclude imports of an unpatented or unpatentable drug product (for example, a naturally occurring protein) if it has been produced abroad using a process that is patented in the domestic market.

Finally, patent protection for pharmaceuticals is affected in some countries, at least in principle, by provisions to issue compulsory licenses in public health emergencies, or in furtherance of other national priorities. (The US has an interesting, but thus far unutilized, provision for “march-in rights” on inventions arising from publicly funded research.)

It is clear, therefore, that a meaningful effort to characterize the strength of IPRs across countries, or to track changes within a given country over time needs to account for many factors. At a minimum, these include the following:

A Non-Comprehensive List of Indicators that may Affect the Strength of Biopharmaceutical IPRs

Term of market exclusivity	Patent term Market exclusivity provided by regulatory approval Patent/exclusivity extensions to compensate for regulatory review delays Extensions for pediatric investigation Extensions for orphan drugs Extensions for drugs targeting specific diseases
Patentability standards	Scope of claims Obviousness/inventive step Utility/industrial applicability Novelty (and grace periods) Priority rules
Patentable subject matter	Products Manufacturing processes Manufacturing intermediates Alternative salts and esters of previously patented compound Use of a product in treating specific diseases Treatment protocols, dosing Packaging/delivery mechanisms Metabolites Naturally occurring substances

	Genomic or biophysical data Physiological pathways Targets/receptors Transgenic organisms
Restrictions on imitators	Ability to block "product by process" imports Ability to block testing of production processes Ability to block stockpiling of patented products by generics in advance of patent expiration Ability to block reimportation/parallel trade
Obligations of patentees	Disclosure requirements (depositing microorganisms or cell cultures, genetic sequences, best mode etc.) Compliance with competition policy (or exemptions) Disclosure of the origin of genetic resources or traditional knowledge
Enforcement/challenge mechanisms for all IPRs	Preliminary injunctions: availability/standards Presumption of validity Recovery of lost profits Recovery of "reasonable royalty" Punitive damages: how much, when awarded Judicially applied limitations on enforcement Criminal counterfeiting: penalties, burden of identifying, prosecuting, etc. Incentives to challenge patents e.g. Hatch-Waxman Pre/post grant opposition
Trademarks	Protection of brand names Protection of "trade dress"
Copyright	Marketing/training materials
Data exclusivity	When/if imitators can rely on innovator's submission of safety/efficacy data When/if imitators can rely on innovator's submission of manufacturing data
Database protection	Proprietary collections/linking of physical, genomic, epidemiological data
Special provisions	Government rights in inventions arising from publicly funded research Research exemptions Prior user rights Compulsory licensing in public health emergencies Compulsory licensing for other reasons Exclusive marketing rights under TRIPS
Bilateral treaty provisions	Other restrictions or exemptions specific to products of certain countries

To my knowledge, only Pugatch (2006) has worked on an index based on such a comprehensive set of indicators for assessing the strength of IPRs in this sector. Since the passage of the TRIPS Agreement, many countries have made significant changes to their patent laws in various of the dimensions listed above, and the diversity of these changes across countries presents interesting potential opportunities to identify their effects. Obviously, though, the effort required to collect data on all of these items is high: Pugatch has computed his index only for eight countries. There are also a number of methodological issues, as with all such indexes. First, to be useful in empirical analysis, component items must be aggregated to some extent, and such aggregation involves applying weights to the components and categories. Pugatch proposes an ad hoc scheme, based on his assessment of "core", "significant" and "added-value" components, though clearly the most informative weighting is a matter of empirical investigation. Second, there is the question of whether to score the components based on *de facto* vs. *de jure* criteria: "paper" availability of rights or procedures may mean very little in terms of practical, concrete implications for patent holders or consumers.

It should, therefore, be a priority to construct (and publish) this type of index for a wide range of countries; to do this both on a “look back” and continuing basis, e.g. 1990, 1995, 2000, 2005, 2010, and to use a similar methodology to construct indexes relevant to other sectors, e.g. the complex/cumulative technologies such as software, telecommunications, semiconductors.

In addition, it would be helpful to supplement this type of index with a more subjective, summary approach based on surveying stakeholders. Surveys of R&D managers in the US and other OECD countries (Levin et al, Cohen et al, EU Community Innovation Survey) have been very informative about business decision-makers’ evaluations of the competitive impact of IPRs, and remain the only way of assessing (a) the importance of other appropriability mechanisms and (b) stakeholder perceptions of the *de facto* strength of IPRs. It would surely be helpful to collect such data on perceptions of the strength of IPRs in this sector and others on a regular basis by surveying/interviewing stakeholders in a range of countries. (See, for example, the surveys conducted by Lanjouw and Cockburn (2001) and Lanjouw and MacLeod (2005) and Gehl Sampath (2005) in India). An alternative and very interesting approach is that of Sherwood (1997) who presented subjective estimates of the strength of IPRs in 18 different developing countries in the mid-1990s based in large part on his personal experience working as a practitioner in this area.

2.2 Pricing

Remarkably little is known about international differences in the pricing of pharmaceuticals and their relationship to IPRs. Reliable data are very difficult to find outside the OECD countries, and even within the OECD, cross-country comparisons are difficult to perform. Danzon and Kim (1998) highlighted the substantial methodological difficulties inherent in comparing drug prices across countries, concluding that highly misleading results could be obtained unless comparisons are based on a comprehensive or representative sample of products, and price differences are appropriately weighted using standard index number methods. However, because of variation in packaging, formulation, dosage forms and strength, assembling large enough representative samples of comparable products is very difficult and most published research has focused on small numbers of drugs and small numbers of countries.

Critically, “list” prices of branded products are likely to be a very poor guide to prices actually paid by consumers and other payers in both developed and developing countries. Government procurement or negotiations by other large purchasers such as insurers are known to result in very substantial “invisible” discounts. Even where discounts are not present, manufacturers’ selling prices are only one component of the prices faced by end-users which often include substantial distributor and retailer margins, import duties, taxes, etc. Yet, data on actual transaction prices (and sales volumes) are not easy to obtain. Commercial market research firms such as IMS and Frost & Sullivan attempt to collect this type of data for a wide range of countries, but, as they are not easy for noncommercial users to obtain, their reliability is very difficult to assess.

The World Health Organization (WHO) and some nonprofit organizations have supported collection and publication of prices of selected drugs. Once such effort is the “spectrum of prices” of essential drugs published in the International Drug Price Indicator Guide (MSH (2007)) since 1986. Other initiatives are limited to specific drug classes, such as MSF’s Guide on ARV Prices, or the various catalogs and price-reporting mechanisms sponsored by WHO for tuberculosis, malaria, and HIV/AIDS. As an alternative, WHO has endorsed an effort in conjunction with an NGO (Health Action International) to assemble a database on prices of a relatively small “core list” of drugs in a wide range of countries, built from voluntary surveys conducted by NGOs,

government agencies, academic researchers and other interested parties (WHO/HAI (2003)). This project is potentially very useful, and reports submitted to date by participants provide interesting and valuable information on price dispersion, notwithstanding the difficulty of assessing the reliability and comparability of data collected from such heterogeneous (and self-selected) sources. Unfortunately, the complementary data on consumption volumes needed to construct price indexes – the most economically meaningful basis for making price comparisons across countries – from either of these sources are not readily available.

Even where price data have been obtained for a wider range of countries, great care must be taken to control for institutional differences in procurement, distribution and price regulation schemes. For example, Borrell (2007) conducted an unusually careful study of pricing of drugs used in ARV “cocktail” therapy for HIV/AIDS in 34 countries, finding substantial variation across and within countries, but was unable to fully control for “noise” in prices induced by off-invoice discounting by manufacturers and the impact of subsidized or donated supply and other factors. Notwithstanding these measurement difficulties, Borrell found that prices of these drugs were higher in countries with product patents for pharmaceuticals. This paper is exemplary in using a “quasi-experiment” methodology (see Meyer (1995)) based on assigning drug-country pairs to treatment and control groups which minimizes potentially important biases induced by the endogeneity of patenting decisions, and in carefully controlling for certain types of omitted factors using country and year fixed effects and interactions. It would certainly be worthwhile to test the robustness and generalizability of these findings by extending this study to more drug classes and more countries, and with price data obtained from alternative sources.

One important source of evidence on the relationship between patent protection and prices may be the impact of patent expiration and generic entry. In countries such as the US, with relatively little price regulation and a very competitive generic industry, patent expiration normally results in rapid entry by generics and substantial losses in market share for the brand. (See Caves, Whinston and Hurwitz (1991), Griliches and Cockburn (1995), Frank and Salkever (1997), Grabowski and Vernon (1992), Reiffen and Ward (2005), Scott Morton (2000) and others.) The substantial brand-generic price differences that emerge in these circumstances suggest that pharmaceutical prices may be much higher when protected by product patents than would otherwise be the case. But it is critically important to be careful about the counterfactual: almost all of these studies are of the US market, and reflect a specific competitive environment, regulatory provisions that promote generic entry (the Hatch-Waxman framework, see Grabowski and Vernon (1996)) and substitution of generics for brands, limited government purchasing or price regulation and a very large market size. In other developed countries with different institutions and industry structure, generic competition is often muted, and brand-generic price differentials can be much smaller (see Pammolli, Magazzini and Orsenigo (2002)). Unfortunately, very little is known about industry structure, regulation, and generic pricing and entry outside the OECD countries.

In some countries, an important source of competition for branded products is supply under compulsory licensing provisions, or imports of the branded product by third parties through parallel trade or “reimportation” (Scherer and Watal (2002)). These mechanisms – or the threat to resort to them – are occasionally used by governments to try to lower domestic prices and improve access. Compulsory licensing can also occur as the outcome of enforcement of competition policy provisions. However, the impact of these mechanisms can be difficult to gauge. Where issuance of compulsory licenses results in a highly competitive supply of generics, substantial price declines can be expected. Watal (2000) suggested price declines of 90 per cent for some drugs in India under a compulsory licensing regime. However, if issuance of a compulsory license does not result in vigorous generic competition, then the outcome can be that prices are somewhat lower, but not substantially lower, than those set by the patent holder – and the primary impact of the compulsory license being to shift profits among suppliers.

Parallel trade is also a potentially powerful way to reduce domestic prices by allowing imports from lower-priced markets. Again, the impact of parallel trade can be difficult to assess. In some cases, parallel trade does appear to have lowered prices of some drugs in some countries quite substantially. But arbitrage between markets does not necessarily drive prices down to the level of the lowest-priced market unless the manufacturer is willing to supply unlimited amounts, and there is some evidence that the major beneficiaries of parallel trade in pharmaceutical products are intermediaries and arbitrageurs rather than final purchasers in the importing country (see Kyle (2007a), Ganslandt and Maskus (2004) and Kanavos *et al* (2004)). Most of the work in this area has focused on the developed countries, and beyond some highly publicized cases, mostly involving HIV/AIDS drugs, there is relatively little systematic evidence on the impact of compulsory licenses and parallel trade on pharmaceutical prices in developing countries and smaller markets.

For some countries and diseases, donated or subsidized supply may be a significant portion of the total market. IFPMA (2007) catalogued large numbers of programs in which commercial entities supply free or low-cost products. There are also significant efforts by governments and private philanthropic entities to supply drugs and vaccines in various countries. These efforts may have significant economic impacts on the pharmaceutical market, for example by effectively segmenting the market on the demand side, or by impacting the commercial environment for for-profit distributors.

Data on these demand-side factors is not widely available. Donated or subsidized supply is very difficult to track in conventional economic data since it does not flow through normal commercial channels. The same holds for government procurement, which is rarely transparent. Assessing the nature, and impact of price regulation schemes is particularly challenging. Jacobzone (2000) is one of the only published sources to systematically catalog and compare price regulation schemes across countries (though confined to the OECD countries). Lanjouw (2005) collected summary information on price regulation for a wider range of countries. However, it is very difficult to characterize price regulation schemes without in-depth country-specific knowledge of the relevant institutions and practices, and even more difficult to construct measures of their impact on prices that are comparable across countries.

While prices are likely to be an important determinant of access to drugs, consumption may also be stimulated by marketing and promotional efforts or constrained by other demand-limiting factors. Marketing and promotion of pharmaceuticals is generally believed to have a significant influence on consumption, but is a complex phenomenon: many countries regulate marketing of pharmaceuticals. For example, in some countries, marketing is only permitted if directed solely at physicians and other prescribers; in others consumers can also be targeted. Some countries closely monitor the content of advertising messages. Almost all the research on this topic has focused on the influence of marketing on the behavior of physicians in high income countries. Very little is known about the impact on drug consumption patterns of marketing by commercial and non-commercial entities in middle- and low-income countries (see the comprehensive review by Norris *et al* (2004)).

While marketing may increase drug consumption, a variety of institutional factors can restrict it. These include restrictions on what drugs are provided by national health care systems or are eligible for reimbursement under public or private insurance, limits on access to health care providers, the pricing and availability of complementary technology and services (e.g. diagnostic equipment or testing services) and the pricing and availability of substitute forms of treatment.

Finally, very little is known about the economics of the distribution system for pharmaceuticals. The supply chain for these products is complex and subject to varying degrees of regulation in different countries. The competitiveness and efficiency of wholesale and retail distribution may be very important determinants of the price of drugs to end-users: in general, it can be expected that a highly regulated and highly concentrated supply chain will result in very high markups and inefficiencies, leading to high retail prices regardless of the patent status of products flowing through it.

Economic studies of the welfare impact of higher prices of pharmaceuticals (the assumed consequence of strengthened IPRs), therefore, face a number of challenges. Critical parameters in many of the studies which have attempted to predict the impact of introducing IPRs on both price levels and consumer welfare are price elasticities, about which very little is known. Subramanian (1994), Maskus and Eby Konan (1994), Watal (2000) and Fink (2001) attempted to compute the welfare impact of introducing IPRs for pharmaceuticals using varying degrees of sophistication in modeling industry structure, but rely crucially on assumptions about substitution between patented and non-patented drugs that would need to be tested empirically.

Very few studies have attempted to estimate price elasticities econometrically, and almost all of these have used data on the US market (see for example, Ellison *et al* (1997), Cleanthous (2003), Crawford and Shum (1999), Rizzo (1999)). For emerging markets, the single exception of which I am aware is the ambitious paper by Chaudhuri, Goldberg and Jia (2006) which takes on the challenge of estimating a demand system for a set of closely related drugs (fluoroquinolones) using Indian data. The very substantial negative impacts on welfare predicted by the model have attracted much attention. But it is important to note that these estimates were obtained using quite restrictive assumptions on functional form and identification, suggesting that additional econometric demand studies in emerging markets would be very helpful to put this result in context. Particularly useful would be studies of a wider range of drugs (e.g. those used for chronic as well as acute conditions), exploration of different functional forms (e.g. logit), and use of natural experiments or convincingly exogenous supply shocks for identification.

It may also be important to recognize consumer heterogeneity in these models. It has been suggested, for example, that in low- or middle-income countries “open market” transactions are priced based on demand from a small number of wealthy consumers, and that income distribution within a country is, therefore, an important factor (Wong (2003)).

2.3 Access and Availability

In addition to any effect on pricing of pharmaceuticals, IPRs may also have an important effect on health and consumer welfare by promoting more rapid diffusion of new drugs across countries. Studies of the timing of new drug launches across countries such as Kyle (2006) and (2007b) and Lanjouw (2005) show that there can be long delays before newly approved drugs become available outside the country in which they are first approved. Indeed in many instances, new drugs are never launched in a country. Kyle (2006) looked at drug approvals in the G7 countries and found that fewer than 4 per cent of “opportunities” (i.e. distinct instances of country/molecule/therapeutic class) to launch drugs were actually exploited. Lanjouw (2005) examined this phenomenon for a much larger set of countries, and focused on the influence of IPRs and price regulation, finding that in countries with weak IPRs and aggressive price regulation new drugs become available for sale (if at all) only with substantial delays.

However, identification of these temporal and geographic “gaps” in availability of new drugs is not straightforward. Because a single new active ingredient may be sold in a variety of chemi-

cally distinct yet clinically highly similar variations, or sold in combination with other drugs, or sold under different names, simply establishing whether or not a new drug is being marketed in a given country can be formidably difficult. Neither is it clear how to establish the timing of when a drug becomes available: historical records on regulatory approval are difficult to access, and regulatory approval may not correspond to the drug actually being distributed.

Even if these data issues can be resolved, it is important to control carefully for differences across countries on a number of dimensions other than IPRs and price regulation: “market size” in the sense of income, population and health care expenditure clearly affect incentives to launch products, and at the level of specific diseases, prevalence, national conventions for medical practice, and availability of complementary technology also play an important role. Kyle (2007b) also identified an effect on the extent and timing of drug launches of variation in the capabilities and experience of the innovator company.

Conclusions about the impact of changes in IPRs on pricing and demand are difficult to reach without (1) reliable data on pricing and consumption across a wide range of drugs and (2) adequate controls for other factors affecting demand. There are a large number of open, important and factual questions about international differences in pricing, distribution and consumption of pharmaceuticals. What is the price of large “baskets” of directly comparable pharmaceutical products (appropriately weighted to reflect actual consumption patterns or “public health weights”) in high-, middle- and low-income countries, and how has the price of these baskets changed over time within countries? Are these price levels and trends different for off-patent vs. patented products? How much intra-country dispersion is there in pricing, and how much does pricing vary across different distribution channels (retail pharmacy, hospital, public/voluntary sector)? To what degree do manufacturers or other participants in the distribution chain engage in intra-country price discrimination, and on what basis? Within a given country, what are the components of prices (manufacturer selling price free on board (FOB) at the shipper’s location) and (inclusive of carriage insurance and freight (CIF) to the customer), local wholesaler acquisition price gross of tariffs or customs duties paid on imported products, distributor margin, retailer margin, dispensing fees, retail sales taxes, etc.)?

In addition to these factual questions about pricing, it is very important to identify aspects of the regulatory and policy environments which influence pricing and consumption. These include price controls or other forms of price regulation which can take a wide range of forms, such as direct price controls or regulation of margins at various points in the distribution chain, regulation of rates of return, price controls based on benchmarking of manufacturer prices against comparator countries (“international reference pricing”), therapeutic reference-based pricing schemes (such as those used in Australia, Germany and some parts of Canada) which cap insurance reimbursement within a therapeutic class at the price of a reference drug. Other important aspects of domestic pharmaceutical policy or market institutions include limits on access or consumption of drugs via formularies or other constraints on prescribing under government health plans or private insurance, utilization caps or reimbursement limits placed on specific drugs and operating on prescribers or patients, legal or regulatory frameworks that permit or encourage therapeutic substitution among drugs or brand-generic substitution within drugs by dispensing pharmacists.

2.4 Research and Development

As with the demand side of the pharmaceutical market, a paucity of reliable, detailed data has limited research on the impact of IPRs on R&D in pharmaceuticals. At least as far back as Taylor and Silberston (1973) surveys of industry participants about the impact of patents on R&D incentives have found the pharmaceutical industry to be critically – and almost uniquely –

dependent on patent protection.¹ Other such surveys include Mansfield (1981), and more recently, Levin *et al* (1987) and Cohen *et al* (2000) and the various Community Innovation Surveys conducted in EU member states since the early 1990s. In these surveys, pharmaceutical companies show a very high propensity to patent, and research managers typically report that patents are very important to securing competitive advantage, or would reduce R&D by a very large fraction (>50 per cent) if patent protection for pharmaceutical products were removed. Some surveys connecting R&D incentives to patent protection outside the high-income countries have been conducted, but these are difficult to access, have not been published in international peer-reviewed journals and are not widely discussed. Lanjouw and Cockburn (2001) and Lanjouw and MacLeod (2005) reported results from surveying relatively small samples of managers of Indian pharmaceutical companies which suggest some sensitivity of R&D spending and project choices to the prospect of patent protection. However it is difficult to generalize from the case of India (which has a relatively large and well-established domestic pharmaceutical manufacturing industry) to other countries. There are also obvious difficulties inherent in trying to determine the impact of IPRs on R&D incentives through such surveys in circumstances where domestic R&D capabilities have yet to develop -perhaps because of historically weak or absent IPRs or other factors.

Broad-based statistical studies of the impact of changes in patent protection on R&D have found mixed effects. In an exemplary study, Qian (2007) found little evidence of a correlation between the strength of patent protection and a number of indicators of domestic innovation in pharmaceuticals in 92 countries, using a careful econometric methodology to control for other differences in country characteristics. Case studies of the impact of changing IPRs on pharmaceutical R&D expenditure in specific countries have found a range of effects. Scherer and Weisburst (1995) found no clear effect of introducing pharmaceutical product patents in Italy in 1982. However, introduction of a compulsory licensing regime in Canada in the 1970s resulted in a dramatic reduction in the amount of pharmaceutical R&D conducted in Canada, and its removal in the 1990s had an equally substantial positive effect (Padzerka (1997)). Indirect measures of the impact of changing IPRs on the profitability of R&D, such as estimates of the differential effect on stock market valuation of R&D-based pharmaceutical firms vs. manufacturing-oriented firms, suggest quite substantial effects in some countries (La Croix and Kawaura (1996), Kawaura and La Croix (1995)).

However, it is difficult to generalize from these episodes, particularly to countries with very different income levels or countries with very little existing R&D capacity. Furthermore, the innovation process in this industry is increasingly complex, organized on a global scale, and involves a wider range of actors from both the for-profit and non-profit sectors, and the impact of changes in IPRs in a specific country on R&D incentives perceived by a pharmaceutical company is, therefore, increasingly difficult to assess. Beyond the most obvious – R&D expenditure – several distinct areas of potential impact of IPRs on the innovation process can be distinguished.

2.4.1 *Level of R&D Expenditures*

In some circumstances, it is reasonable to expect that changes in a country's IPRs affecting pharmaceuticals will result in changes in R&D spending, and efforts to track R&D expenditures by domestic firms, receipt of payments for contract R&D, venture capital investments and other sources can be a useful indicator. It may also be useful to look at complementary forms of R&D investment, particularly by government or other non-profit actors in the form of direct expenditure, subsidies, grants, or investments in public-private partnerships (PPPs.) Even in countries with highly developed national statistical systems, consistently tracking the full range of such expenditures over time can be very difficult due to changing definitions of R&D or changing sampling methodology. Identification of any impact of changes in IPRs on R&D spending may

therefore require the development of original datasets from primary sources such as company financial reports (see, for example, Arora *et al* (2008)).

However, even with comprehensive, high-quality data, the linkage between domestic IPRs and R&D expenditure may be difficult to observe in aggregate data, or for companies operating globally, or making the bulk of their sales outside the domestic market. The marginal impact of changing IPRs in a specific country on a global company's R&D incentives may be so small as to have no distinguishable impact on the overall R&D budget, or it may be significant, but "swamped" by other considerations, or its effect may be felt only gradually over time.

2.4.2 *Location and Composition of R&D*

Rather than looking to changes in the overall level of R&D spending, the impact of changes in IPRs may be most visible in their influence on the location and composition of the global R&D effort. Though pharmaceutical companies have always been able to operate R&D facilities largely independently from other activities, increased vertical dis-integration in R&D activities since the mid 1980s has further relaxed organizational constraints on the location of research activity, permitting extensive geographic reorganization of R&D across countries and regions, as well as vertical reorganization within firms. In the US, for example, "upstream" firms specializing in new technologies for drug discovery are now often located in different locations (such as Boston and the San Francisco Bay area) from those historically used by the "big pharma" firms concentrated in Philadelphia, New Jersey, Connecticut and the mid West.

Many factors drive these R&D location decisions, and the observed geographical distribution of research reflects complex tradeoffs among them. On the one hand, economies of scale and scope in performing R&D, the presence of internal knowledge spillovers, and costs of coordinating activity across dispersed units suggest that, all else equal, firms should limit geographic dispersion of R&D. Furthermore, some locations may be more intrinsically economically attractive because of lower costs, access to government subsidies or favorable tax treatment of R&D. Proximity to centers of academic excellence and other forms of non-commercial research also appears to convey benefits such as raised research productivity, see Furman *et al* (2006). On the other hand, these economic forces tending to concentrate R&D can be offset by the impact of public policy choices that give pharmaceutical companies strong incentives to maintain domestic R&D spending. For example, some countries, such as the UK, have explicitly linked the stringency of price regulation to local R&D spending levels (Bloom and Van Reenen (1998)). In other cases, such as Canada, local R&D spending has reflected an explicit political bargain to avoid compulsory licensing.

Historically, the US has been perceived by the industry as a very attractive location for pharmaceutical R&D because of its very limited use of price regulation and government purchasing, and strong patent rights. In contrast, in the late 1990s, EU governments became very concerned (see Gambardella *et al* (2000)) that overly aggressive price controls and hard bargaining by state purchasers were driving away investment in pharmaceutical R&D and adversely affecting the competitiveness of EU based companies, though there is little evidence of any major shift in R&D spending away from Europe. Episodes such as Canada's experience with compulsory licensing of pharmaceuticals in the 1970s and 1980s, or more recent examples such as the periodic heated disputes between OECD based companies and governments of developing countries over pricing of anti-retroviral drugs suggest that R&D location decisions may be quite sensitive to government policies directed at lowering the cost of acquiring pharmaceuticals. On the other hand, studies such as Chien (2003) of specific compulsory licenses suggest a muted response, if any, and critics of the industry argue that gains from lower prices more than offset any negative domestic impact from compulsory licensing.

Countries such as Australia, which have relatively stringent drug price controls, continue to face major challenges in attracting significant R&D investment by multinational drug companies, in spite of strong academic research capabilities, an attractive business environment and substantial public support of commercial biomedical research (Rasmussen (2003)). There is, however, little statistical evidence establishing strong causal relationships between the stringency of price controls and R&D location decisions.

Beyond these “price” drivers, several other factors have been identified as influencing R&D location decisions. These often work through indirect or unpriced effects such as knowledge spillovers that are conveyed by “open” publications, geographic proximity, or communication through informal professional networks rather than through economic transactions. For example, drug discovery laboratory sites tend to specialize in therapeutic areas or scientific disciplines and since proximity to publicly funded science appears to be an important determinant of research productivity, these often reflect local academic centers of excellence in particular fields. Furman *et al* (2006) showed that patenting by pharmaceutical companies is positively correlated with the volume of academic publications by “local” public sector scientists. The very substantial levels of publicly funded biomedical research in the UK, the US, and some other countries has, therefore, played an important role in sustaining similarly high levels of commercial investment in drug discovery in these countries.

More generally, like other knowledge-intensive activities, discovery research appears to display substantial agglomeration externalities. Drug discovery activity tends to “cluster” in a small number of locations around the world: many major discovery laboratories are located in New York/New Jersey/Connecticut SMSA, Boston, the San Francisco Bay area, the suburbs of Philadelphia, the Research Triangle in North Carolina, the Rhine Valley, the suburbs of London, Stockholm and Tokyo/Kansei.

These are conspicuously not low-cost locations, so this clustering suggests substantial offsetting economic benefits derived from being co located with other firms. Beyond the role of localized knowledge spillovers, benefits from co location with other pharmaceutical firms include access to skilled labor and “infrastructure” in the form of specialized services and suppliers, and efficient interaction with collaboration partners.

The final factor that may affect R&D location decisions is the strength of IP protection. Though there is no obvious connection between the degree of patent protection in the local product market and the productivity of R&D conducted in any given country, the nature of a country’s IPR regime appears to affect multinationals’ willingness to conduct R&D activities there. (See Arora, this publication, Branstetter, Fisman and Foley (2006), Smarzynska Javorcik (2004)). This may be because weak patent protection for products often correlates with weak legal protection of other forms of intellectual property such as trade secrets and associated contractual agreements with employees and suppliers, and limited avenues to enforce these rights. Both patent and non patent protection of intellectual property play an important role in maintaining exclusive access to, and control over, proprietary knowledge, and in countries with weak intellectual property, companies may have well-founded concerns about “leakage” of valuable information to local competitors. Unfortunately, summary indexes of IP protection such as the Ginarte Park indexes give only a partial view of appropriability conditions, and, therefore, cross-country regression analyses based on such measures cannot easily address these issues.

Zhao (2005) argues that weak IP regimes need not deter R&D investment by multinationals: in the absence of strong IPRs, companies can nonetheless develop alternative mechanisms for realizing returns on innovation and intellectual property. These mechanisms include rapid “internalization” of knowledge through efficient internal organizational processes and control of

complementary assets, and may make it possible to profitably exploit low prices of R&D inputs and under-utilized domestic innovation capabilities. However, this argument is most appealing for technologies that have a substantial tacit component, are strongly complementary to other protected assets held by the firm and have rapid development cycles. This is not the case for pharmaceutical R&D, where results from R&D are often easy to “externalize” and imitate, and product lifecycles are measured in decades.

Not surprisingly, therefore, R&D activity in pharmaceuticals has historically been concentrated in countries with strong and enforceable intellectual property and has only just begun to grow in countries that have recently adopted OECD-style patent systems under the provisions of the TRIPS agreement. It is, of course, difficult to assign causality from such observations: it may be that IPRs have been implemented or strengthened most quickly and extensively in those countries where the domestic pharmaceutical industry has greater influence on political processes. Nonetheless, political choices to subsequently weaken or limit patent protection on pharmaceutical products may have serious consequences for the development of nascent research sectors in some countries.

In India, for example, Arora, Branstetter and Chatterjee (2008) show a surge in R&D investment and in stock market valuation of research intensive companies, but it remains to be seen whether this trend is sustainable.

Proxy data on R&D activity, such as the location of inventors listed on US patent applications or PCT filings (see Cockburn (2008)), or location of clinical trial sites (see Thiers, Sinskey and Berndt (2007) and Berndt, Cockburn and Thiers (2008)) point to increasing geographic dispersion of R&D. This is at least correlated with the presence of IPRs, with the greatest growth in these measures occurring in countries which adopted stronger IPRs for biomedical inventions, even after controlling for other country attributes, such as costs of conducting clinical trials, GDP, medical infrastructure, human capital, and “e readiness.” However, it is difficult to find a strong causal relationship in econometric tests of these relationships, and difficult to distinguish “pull” factors, such as lower costs or higher anticipated profits, from “push” factors, such as saturation of clinical research capacity in traditional locations.

Development of better data on R&D activity in this sector at the country level, particularly on contract and collaborative research arrangements, would be very helpful as would further detailed country studies such as Arora, Branstetter and Chatterjee (2008). Very little is known, for example, about the nature and extent of pharmaceutical R&D activity in China (which is widely believed to be likely to become a significant player in biomedical R&D) or in many other developing countries.

A final area where IPRs may have an impact on R&D is on the composition of expenditures. Incentives to develop drugs for specific diseases are clearly affected by the prospective profitability of these markets, which is a function of anticipated market size and margins to be realized from serving them. It has often been observed that the bulk of innovation in pharmaceuticals has been targeted at the “large” markets created by the combination of patent protection with population size, income and disease incidence in OECD countries. In contrast, a very small fraction of the global R&D effort has been directed at diseases which are “small” markets in the sense of being relatively rare, or prevalent in low-income populations or in countries with limited profit potential. Patent protection can, therefore, play a significant role in driving the composition of R&D if it effectively increases market size for neglected diseases. Lanjouw and Cockburn (2001) found some evidence that the prospect of IPRs in developing countries was stimulating R&D expenditure in the mid-1990s on tropical diseases prevalent in countries which had previously lacked patent protection. In a more recent study using IMS R&D Focus, a com-

mercial database of R&D projects, Kyle and McGahan (2008) found similar results, though the effect is smaller than the association that they found between strengthening of patent rights in countries where neglected diseases are most prevalent and the number of R&D projects conducted on “global” diseases, for which the largest markets are in the developed countries. This is an issue which surely merits further study. More generally, looking beyond neglected tropical diseases it may also be the case that changes in the IPR regime in countries with patterns of disease incidence that are different from those of the historically patent-protected markets may have substantial effects on the composition of the global R&D budget.

Alternative models for providing incentives to conduct R&D on neglected diseases such as Advance Market Commitments have overshadowed IPRs in recent policy debates. This is a complex and interesting topic, see Kremer (2001) and Berndt *et al* (2006), and careful studies of how alternative incentive schemes such as AMCs work in practice would be useful. Interactions between AMCs and IPRs are poorly understood: while AMCs or other alternative mechanisms may be necessary to support investments in R&D directed at economically unattractive markets, patents may nonetheless play an important complementary role, or may be completely unnecessary (see Maurer *et al* (2004)).

2.4.3 IPRs and the Market for Technology

IPRs clearly play a critical role in facilitating transactions in a “market for technology” that has come to play a central role in innovation in pharmaceuticals.

While this sector continues to be dominated by large integrated firms that conduct much of their innovative activity in house, recent decades have seen significant vertical restructuring of the industry and these firms increasingly rely on externally sourced R&D in both the discovery and development phases of research. In drug discovery, an active entrepreneurial sector that bridges academic and publicly funded research and industrial science has become a very important supplier of drug candidates and tools for performing R&D. In the development phase, specialist firms (contract research organizations (CROs)) now play a significant role in conducting clinical trials on behalf of the sponsor of a drug. The causes of this restructuring of R&D activity are complex, ranging from changes in patent law and practice that have extended exclusionary IPRs into “upstream” science, financial market innovations that have eased access to capital for early stage companies, and the development of institutions that have encouraged universities and public laboratories to actively promote commercialization.

One consequence of these changes is that pharmaceutical innovation now relies heavily on a complex web of contractual agreements linking a variety of actors at various stages of the drug development process. Danzon *et al* (2005) found that over one-third of new drugs approved between 1963 and 1999 originated in alliances between industry participants. Data on strategic technology alliances also shows an explosion of collaborative activity in the biomedical sector since the early 1990s, with many of these alliances spanning national boundaries.

While IPRs are often thought to support markets for technology, a counter-argument is often made that proliferation of patents may “choke” biomedical innovation by raising transaction costs (see Heller and Eisenberg (1998)). However, evidence on these issues is mixed: Walsh *et al* (2004) surveyed life scientists and found few adverse effects of patents. On the other hand, in one interesting study (Murray and Stern (2006)) patents were shown to negatively affect researchers’ access to knowledge, as measured by citations. It would certainly be interesting to conduct similar studies of researchers located in emerging or transition economies, where the institutions of “open science” may receive different levels of funding from non-commercial sources, or operate within a different innovation system and cultural milieu.

A related issue, and another comparatively neglected area of research, is the contribution of the natural genetic and biological resources and associated traditional knowledge of developing countries to biomedical research. Anecdotal evidence suggests that the origin of many important pharmaceutical products can be traced back to such resources. However, there is very little systematic empirical work on this topic, and beyond the reporting of opportunistic attempts to obtain patents in the US on various traditional medicines, little analysis of the role of IPRs in promoting (or hindering) access to an important component of the “research commons”.

IPRs play a critical role in facilitating and governing transactions in the market for technology (Arora, Fosfuri and Gambardella (2001)). Technology licensing, collaborative R&D, and contract research are very difficult to sustain on a commercial basis without well-defined and enforceable rights over research results. It is widely believed, therefore, that strengthening IPRs will not just promote domestic R&D activity, but will also stimulate trade in technology. However, direct evidence on these types of international technology flows is very difficult to measure in many contexts. License agreements and similar contracts provide one indicator, but licensing of technology is notoriously opaque, since firms rarely publicly disclose licensing transactions. Some licensing payments are tracked in trade statistics: Branstetter, Fisman and Foley (2006) use trade data to show how licensing payments received by US multinationals from their foreign affiliates changed following patent reforms. However, non-priced licensing transactions (such as cross-licenses) are largely invisible.

Further, royalties paid under license agreements are only one indicator of technology transfer. Patent citations have been widely used to track knowledge flows (Jaffe and Trajtenberg (2002), Peri (2005), Keller (2002)) but there are obvious endogeneity problems in using patents to track the impact of changes in IPRs, and such studies typically are restricted to citations made within the USPTO or EPO systems. One important mechanism may be strategic partnerships, joint ventures and collaborative agreements. Some, but not all, of such agreements are tracked in databases, but their purpose and the amount of resources involved are often difficult to determine. The picture is further complicated by parent-subsidiary relationships, and the possibility that economic flows are driven by tax and transfer pricing concerns.

2.5 Trade and Production

IPRs may also play a role in driving patterns of trade and the national and international structure of production. Zuniga and Combe (2002) found dramatic changes in the industrial structure of pharmaceutical manufacturing in Mexico following the strengthening of IPRs on pharmaceuticals in the early 1990s. Similar “shake out” processes of consolidation among domestic manufacturers, and acquisition of domestic producers and “greenfield” FDI by foreign producers are apparently occurring in India and other countries, but are poorly documented.

Changes in the IPR regime may also be associated with a country’s greater involvement in manufacturing and trade of pharmaceuticals and other knowledge-intensive goods. Delgado, Kyle and McGahan (2008) found that global trade in pharmaceuticals and related products has increased since the passage of the TRIPS agreement, relative to sectors identified as being less affected by its provisions. Koenig and MacGarvie (2008) found evidence that differences among European countries in the regulatory environment for pharmaceuticals influence foreign investment in manufacturing and marketing facilities, suggesting that variation in IPRs might have a similar impact in a wider sample of countries. Ahlering (2004) found little relationship between IPRs in a given country and the share of a pharmaceutical company’s employment in that country, after controlling for “regulatory stringency”, though in a relatively small sample of countries.

3. A RESEARCH AGENDA

Our understanding of the influence of IPRs on the world pharmaceutical industry would be advanced by research in all of the areas discussed above. There are numerous opportunities to inform policy using a variety of methods and approaches, conducted at a variety of levels. Informative methodologies include case studies, surveys and interviews, compilation and publication of high quality data sets and econometric modeling. Levels of analysis range from individual suppliers, distributors and purchasers, to country studies, to regional and international comparisons.

3.1 Characterizing Pharmaceutical IPRs

- It should be a priority to develop a comprehensive and multidimensional measure of the formal structure of IPRs in pharmaceuticals for a broad cross-section of countries, as described above.
- Country-based or cross-country surveys of a broad set of stakeholders (e.g. government and academic medical researchers, health care providers, branded and generic pharmaceutical company executives in R&D/marketing/public affairs/legal, import/export companies, wholesalers and retailers of pharmaceutical products, leading law firms) as to their perceptions of the strength and impact of IPRs would provide valuable context for discussion of policy issues, and a basis for measuring the *de facto* rather than *de jure* IPR environment.

3.2 Pricing and Demand

- Efforts should be undertaken to develop and disseminate comprehensive, accurate and well-documented data on pricing and consumption of pharmaceuticals in a large number of high-, middle- and low-income countries. Notwithstanding the importance of diseases or conditions such as HIV/AIDS, malaria and tuberculosis for global public health, and their prominence in public debates, it is important to cover as widely as possible the range of drugs. This type of data should feature:
 - Pricing of large “baskets” of directly comparable pharmaceutical products (appropriately weighted to reflect actual consumption patterns or “public health weights”).
 - Tracking of consumption volumes.
 - Tracking of price levels and trends for off-patent (or multisource) vs. patented (or single source) products.
 - Tracking of dispersion in pricing within countries (e.g. by region, by urban vs. rural etc.) and by distribution channel (retail pharmacy, hospital, public/voluntary sector).
 - Tracking of components of prices faced by consumers or other end-user purchasers, such as manufacturer selling price FOB and CIF, local wholesaler acquisition price after tariffs or customs duties paid on imported products, distributor margin, retailer margin, dispensing fees, retail sales taxes, etc.
 - Tracking of the extent to which manufacturers or other participants in the distribution chain engage in intra-country price discrimination, and among which classes of purchasers (e.g. by income, insurance status, etc.).
 - Evaluation of the extent and quality of information about prices available to institutional or individual purchasers of drugs.
 - Careful characterization of the regulatory and institutional factors influencing pricing of pharmaceuticals:

- * Price controls and other forms of price regulation, including direct price controls, regulation of margins at various points in the distribution chain, rate of return of profit regulation of manufacturers, benchmarking of manufacturer prices against comparator countries (“international reference pricing”) and therapeutic reference-based pricing.
 - * Constraints on access or utilization of drugs through use of formularies or other limits placed on prescribing under government health plans or private insurance, such as quantitative limits placed on the volume of utilization of specific drugs, or reimbursement limits (or financial penalties) based on the volume of drugs prescribed.
 - * Legal or regulatory frameworks that permit or encourage therapeutic substitution by dispensing pharmacists.
 - * Legal or regulatory frameworks that permit or oblige substitution of generics for brands. What are the financial incentives to do so?
- Based on this type of data, analytical investigations of the following pricing issues would be very helpful:
 - Economics of the distribution channel: how do the manufacturer and non-manufacturer components of pricing vary with market structure and competitiveness at different points in the distribution chain?
 - Demand modeling: estimation of demand parameters (price elasticities, substitution, and income elasticities) for a variety of drug classes, using a variety of functional forms and estimation methods.
 - Economics of intra-country price discrimination.
 - Institutional and economic factors promoting or delaying access to newly developed drugs, such as IPRs, price regulation, health and safety approval processes, dissemination of information to prescribers, etc.

3.3 R&D

Studies of R&D and IPRs are generally frustrated by the paucity of consistently gathered and sufficiently detailed data on the full range of R&D activities. Outside the OECD countries, the consistency and quality of data on R&D expenditure is difficult to evaluate, and even within the OECD countries, data published by national statistical agencies is rarely broken down at the level of detail necessary to fully understand the economic and policy issues. Researchers may therefore be able to make major contributions by creating and analyzing data sets that cover the full range of R&D activities, gathered from sources such as surveys, analysis of company financial statements, review of international or local trade publications, or use of indirect indicators of innovative activity such as patent filings in various jurisdictions, publications in scientific journals or listings of clinical trial sites in published study protocols. Important aspects of innovative activity to track include:

- Measures of the volume of R&D activity and transactions in the market for technology as captured by:
 - R&D expenditure by commercial and non-commercial entities.
 - In-licensing and out-licensing agreements and payments.
 - Joint ventures and partnerships.
 - Grants or other forms of support provided to non-commercial entities.
 - Contract research services.
 - Formation of PPPs.
 - Acquisition or spin-out of research-based companies.
 - Investments in and sponsorship of training and skills development.

- Nature and composition of R&D:
 - Pre-clinical vs. clinical research.
 - Disease areas targeted.
 - Scientific disciplines (e.g. molecular biology, medicinal chemistry, process engineering, computer modeling).
 - Medical/scientific specialties (e.g. toxicology, oncology, virology, immunology, cardiology, etc.).

- Beyond the essential task of documenting R&D activity in different countries, and correlating this with the IPR regime, there are many important open research questions in this area:
 - What are the forces driving agglomeration and clustering of R&D activity? What types of government policies spark and sustain development of clusters in this sector?
 - How integrated are world markets for critical research inputs such as highly trained individuals?
 - What are the time horizons over which investments in R&D are planned?
 - What is the relative importance of IPR regimes compared to other factors influencing the location and composition of R&D investments (tax treatment, expected local demand, general business environment, legal system, language, infrastructure and transportation, telecommunications, etc.)?
 - How important is the scale and quality of complementary public sector research and clinical capabilities?
 - Is there evidence that changes in IPRs are affecting access to basic research in emerging and transition economies?

3.4 Trade and Production

Open questions in this area include:

- The influence of IPRs on origin, volume and destination of trade in pharmaceutical products at various stages of the supply chain (finished products, active pharmaceutical ingredients (APIs), intermediates and raw materials).
- The influence of IPRs on intra- or inter-country transfer of process and manufacturing technology, particularly for biotechnology products.

4. CONCLUSION

The pharmaceutical industry is unusually knowledge-intensive, and the economics of this sector are widely recognized to be unusually sensitive to IPRs. Some progress has been made in documenting and understanding the interactions between IPRs, complementary regulatory and policy provisions, the international expansion of the industry, and the implications of these for pricing and access to drugs, R&D, trade and production. However, opportunities abound for developing and analyzing more comprehensive data on this complex and critical sector, particularly in developing countries and countries with economies in transition.

Note

- 1 Valuation studies based on renewal data suggest that patents are unusually valuable in the pharmaceutical sector (Schankerman (1998)).

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COMMENTS ON INTELLECTUAL PROPERTY RIGHTS IN THE PHARMACEUTICAL INDUSTRY: CHALLENGES AND OPPORTUNITIES FOR ECONOMIC RESEARCH

CARSTEN FINK*

Iain Cockburn's contribution provides an excellent introduction to the topic, summarizing the key findings of the available literature, outlining important knowledge gaps and offering sensible recommendations on how these gaps might be filled. I find myself largely in agreement with the views and priorities put forward in Professor Cockburn's paper and will, therefore, use these comments to elaborate on one specific theme discussed in the paper: the incentives for and effects of differential pricing of pharmaceutical products.

Differential pricing structures are sometimes regarded as a way of promoting access to medicines in developing countries without compromising research and development (R&D) incentives. Indeed, such a view is grounded in economic theory. Efficient recovery of fixed R&D outlays calls for discriminatory pricing structures, whereby low-demand elasticity consumers pay more for drugs than high-demand elasticity consumers. Admittedly, free-market discriminatory pricing in segmented markets is unlikely to approximate what economists refer to as Ramsey pricing – which are, after all, regulated prices.¹ Nonetheless, pricing-to-market holds the promise of poor patients being able to afford patented medicines, while encouraging an efficient sharing of global R&D costs.

Questions surrounding differential pricing will arguably become more important in the future. In the mid-1990s, developing countries signed up to the WTO's TRIPS Agreement which requires WTO member governments to protect product patents for pharmaceuticals. However, due to the transition periods in the TRIPS Agreement, developing countries had to (fully) implement the relevant pharmaceutical obligations only by January 1, 2005. In light of the substantial delays between patenting a promising pharmaceutical compound and obtaining marketing approval for the resulting product, the full impact of the TRIPS Agreement will only materialize in the next five to 15 years, as patented products take on a larger share of the pharmaceutical markets in the developing world.

Controversies about pharmaceutical pricing are therefore bound to increase. In principle, countries can resort to compulsory licensing to override the market exclusivity conferred by patents. Indeed, a number of developing countries have done so, mainly for anti-retroviral drugs used in government-run HIV/AIDS treatment programs. In 2007, Thailand broadened the use of this instrument by issuing a compulsory license for a drug to fight heart disease. Such a move appears entirely legal under the rules of TRIPS: contrary to what is sometimes stated in the popular press, the TRIPS Agreement does not confine compulsory licenses to emergency situations.² Selected use of compulsory licensing by individual developing countries is unlikely to alter global R&D incentives.

However, systemic use of such a policy by all developing countries raises a collective action problem. Middle-income countries as a group already account for more than 10 per cent of global pharmaceutical sales and given their faster rates of economic growth relative to developed

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countries, this share is rising continuously (see Fink (2008)). It seems only fair and, indeed, economically efficient for these countries to contribute to the global R&D 'burden'.³ Within the global patent system, such burden sharing can be implemented precisely through differential pricing schemes.⁴

Against this background, what is the evidence on differential pricing? Notwithstanding the substantial methodological challenges in appropriately comparing prices across countries described in Iain Cockburn's paper, some empirical evidence is available. Scherer and Watal (2003) found marked variations in the wholesale prices of 15 anti-retroviral drugs over the 1995-99 period. However, they could not discern any positive correlation between price levels and countries' *per capita* GDP. Wong (2003) confirmed this result using a larger sample of drugs covering seven therapeutical categories between 1994 and 1998. Interestingly, this study found that income-inequality, as measured by countries' Gini-coefficient, has a positive and statistically significant effect on drug prices. At face value, this latter result suggests that pharmaceutical companies take into account local demand conditions in their pricing strategies, but the resulting international pricing structure may not promote broader access to medicine objectives.

At a more anecdotal level, differential pricing according to countries' *per capita* incomes seems more widespread in the case of vaccines and condoms (Scherer and Watal (2003)) – though the characteristics of markets for the latter differ substantially from those of pharmaceutical markets. In the case of drugs fighting HIV/AIDS, tuberculosis, and malaria, several research-based pharmaceutical companies have over the past eight years established *per capita* income-based pricing structures for sales to developing country governments, not-for-profit organizations, and international aid agencies.⁵ Similar pricing policies also exist for other diseases – such as Novartis' International Patient Assistance Program for the cancer drug *imatinib* (brand name: Glivec), which relies on an assessment of patients' means to determine the drug's price.

In summary, available evidence suggests that incentives for differential pricing differ across pharmaceutical products and purchasers. More studies are needed to refine this picture and, in particular, to identify policy measures that may affect differential pricing strategies. The latter include parallel import and price control policies, which may lead to a *de facto* unification of national pharmaceutical markets. From a normative perspective, economists could make a contribution in developing methodologies for calculating globally efficient Ramsey prices in the pharmaceutical sector. Such methodologies could help policymakers in national compulsory licensing and price control policies. By proposing a more objective benchmark of what constitutes 'justified' price levels in poorer countries, they may also serve to reduce conflicts between research-based pharmaceutical companies and pharmaceutical purchasers, which the new IP regime in the developing world will invariably bring about.

Notes

- 1 See Fink (2008) for a discussion of free-market discriminatory pricing vs. Ramsey pricing.
- 2 Emergency situations merely trigger the additional flexibility in the TRIPS Agreement not to seek first a voluntary license from the patent holder before granting a compulsory license. See Article 31(b) of TRIPS.
- 3 LDCs constitute a negligible share of global pharmaceutical sales and, in any case, are still exempted from the TRIPS pharmaceutical patent obligations.
- 4 Even when countries resort to compulsory licensing (or direct price controls), burden sharing is still possible through differential royalties that patent holders receive from generic producers (or differential price controls).
- 5 The relevant price discounts are documented in various editions of the publication *Untangling the Web of Price Reductions* by Médecins sans Frontières, available at <http://www.accessmed-msf.org>. It should be noted, however, that price reductions may have been, at least in part, brought about by competition from generic producers, as most first-line anti-retroviral drugs were still not patent-protected in major developing countries.

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COMMENTS ON INTELLECTUAL PROPERTY RIGHTS IN THE PHARMACEUTICAL INDUSTRY: CHALLENGES AND OPPORTUNITIES FOR ECONOMIC RESEARCH

ROKIAH ALAVI*

Professor Cockburn's paper has touched upon all the key issues related to IPRs in the pharmaceutical industry. It is an interesting and very comprehensive paper. What I intend to do here is to add one additional point that I thought would be useful to be highlighted.

In almost all developing countries that have domestic pharmaceutical production facilities, such facilities are primarily for generic drug manufacturing. As such, these producers mainly benefit from the TRIPS-compliant exceptions and limitations to patents rather than patent protection itself.¹ These exceptions include the "Bolar" provision, permission to utilize clinical test data filed by the patent owner to obtain regulatory approval and compulsory licensing. The concern expressed by many observers is that many regional and bilateral free trade agreements (RTAs and FTAs) are imposing constraints on the use of these flexibilities. Erosion of such flexibilities may have implications on generic drug producers and consequently on prices, competition and access to drugs.

My comments here will focus only on the "Bolar" provision and data exclusivity requirement since issues related to compulsory licensing have been discussed in Professor Cockburn's paper. To obtain approval for a generic product, the manufacturer is required to conduct a study on the formulation of the product, perform stability experiments and undertake bioequivalence studies. The 'Bolar' provision allows generic producers to carry out all these tests, develop the product and submit an application for regulatory approval of a generic product before the expiry of the patent. Thus, it permits a generic producer to market its products soon after the patent expires. Elimination of this provision would mean delays in market entry by generic producers, as they will have to wait until the patent expires before conducting the necessary tests and obtaining regulatory approval.

Data exclusivity refers to the exclusive right granted to innovator companies to prevent the use of their safety and efficacy test data that were submitted to the competent regulatory authority for marketing approval. This exclusive right could be granted to patent owners for a period of time (usually five to 10 years) after obtaining marketing approval.² In most of the developing countries, national laws allow generic drug producers to refer and utilize clinical test data for product approval and registration. Data exclusivity provisions limit the ability of local generic manufacturers from entering the market because they are required to undertake their own clinical tests which are time consuming and costly. Grabowski (2002) estimated the cost of accumulation and compilation of these data to be 467 million US dollars accounting for 60 per cent of total costs of pharmaceutical R&D. Though the exact costs of clinical tests are not known, it is obvious that the amount is very substantial and often beyond the affordability of generic producers in developing countries. Therefore, any initiative to include data exclusivity provisions in patent law is likely to create significant barriers for generic entry. The proponents for data exclusivity claim that the benefits of this provision for developing countries are that it provides incentives for research in identifying new uses for existing unpatented products and encourages the

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innovator manufacturers to introduce and register new products in developing countries (Clift (2007)). In fact, some analysts are recommending a longer data exclusivity period of 12 to 16 years in order to promote investment in research and development in new medicines and new indications for existing medicines (Grabowski (2007)).

The economic literature on the impact of the erosion of TRIPS flexibilities as a result of free trade agreements on the pharmaceutical industry is quite extensive. Generally, most of these studies are qualitative in approach and therefore the findings are not backed by empirical data and analysis. Studies that provide useful and interesting insights into this issue, to list a few, are Pugatch (2004), Kuanpoth (2006) and Baker (2006). The most highly debated and analyzed issue is related to data exclusivity provisions. Almost all studies focusing on developing countries argue that the application of this provision would have a negative impact on them in terms of generic competition and consequently on affordable access to medicines (see, for example, Pugatch (2004), Kuanpoth (2006) and Baker (2006)). Furthermore, some argue that, in developing countries where there is negligible or no innovative pharmaceutical research capability, the prospect for data exclusivity provision to promote research is very limited (Clift (2007)).

Empirical studies are very limited, particularly in developing countries and countries with economies in transition. Nevertheless, there are two interesting empirical studies that have focused on the US-Australia FTA, which might provide some interesting insights for developing countries. Lokuge *et al* (2003) estimated the potential costs of changes in IP provisions under the US-Australia FTA on the pharmaceutical industry in Australia. Using five leading medicines nearing patent expiry as reference, they concluded that generic entry would be delayed by 24 months and, as a result, the additional costs incurred to the Pharmaceutical Benefits Scheme (PBS)³ would be 1.12 billion Australian dollars (approximately 0.67 billion US dollars)⁴ over a four-year period.

Another useful study in this area is a major research project conducted by Thomas Faunce and his team. This project was funded by the Australian Research Council (ARC) in 2005 and it aims to assess the impact of the Australia-US FTA on Australia and the global medicines policy.⁵ Part of that study evaluates the effects of AUSFTA on the activity and returns of innovator and generic manufacturers. The research questions in relation to innovator manufacturers include (1) What are the changes to monopoly rent for patent holders? (2) What are the changes in the number of applications to the Therapeutic Goods Administration (TGA)⁶ and PBS for listing of innovative patented products? (3) What is the impact on research and development investment? (4) What would be the effects on promotion and marketing expenditure? To assess the impact on generic manufacturers, the study planned to evaluate changes in the number of applications for marketing approval and changes to the timing of generic entry. In addition, the study also sought to examine the impact of the AUSFTA on the government's pharmaceutical expenditure; the opportunity costs to other areas of health services as a result of the increase in expenditure on pharmaceuticals; the direct and indirect effects on drug prices; changes in the availability of innovative drugs; changes in the mix of generic and brand name drugs in the Australian market; the impact on out-of-pocket charges and changes in the use of newer innovative drugs compared to existing therapies on the PBS list. Unfortunately, the findings of the study are not available.⁷

The proliferation of FTAs involving developing countries, especially with the US, warrants study on the impact of the erosion of these TRIPS flexibilities on the pharmaceutical sector. There is a need for more concrete empirical research to assess costs and benefits of the changes in the IPR regime. The study undertaken by Faunce *et al* (2005) is an excellent research project that could be replicated for developing countries.

Notes

- 1 Except for when they enter into agreements (e.g. licensing agreements) with larger pharmaceutical companies.
- 2 Note that it also applies to products that have not been patented.
- 3 PBS is a medical subsidy scheme in Australia where from January 1, 2008, patients pay up to only A\$31.30 for PBS medicines or A\$5.00 for concession card holders. The Australian government pays the remaining costs. About 80 per cent of prescriptions dispensed in Australia are subsidised under the PBS. Taken from <http://www.health.gov.au>.
- 4 Based on the 2003 average nominal exchange rate.
- 5 The proposal of this project was published in *Globalisation and Health* (2005), 1:15. The research team included Thomas A. Faunce, Evan Dovan, David Henry, Peter Drahos, Andre Searles, Brita Pekarsky and Warwick Neville. Available at <http://www.globalisationandhealth.com/content/1/1/115>.
- 6 The TGA carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard, with the aim of ensuring that the Australian community has access, within a reasonable time, to therapeutic advances. More details are available at <http://www.tga.gov.au/about/about.htm>.
- 7 It is not known whether this project has been completed.

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