Patenting and Licensing Research Tools

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ABSTRACT

Research tools encompass a wide range of resources, including genes/gene fragments, cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools such as polymerase chain reaction, methods, laboratory equipment and machines, databases and computer software. Access to research tools is integral to advancing progress in biotechnological R&D, in both the biomedical and agricultural sciences. However, a complex web of research tool patents has arisen as a result of the revolution in molecular biology and coincident changes in public policy and patent law. These patents can pose a potential block to accessing research tools. For developing countries, several approaches can be formulated and then implemented in order to overcome potential problems associated with research tools. These include changes in patenting policies, research exemptions in patent law to reduce the risk of infringement in R&D, compulsory licensing to allow access to upstream technologies, and institutional adaptations to facilitate access to needed technologies, such as guidelines intended to promote more appropriate behavior by participants in the system. With carefully formulated, multitiered approaches, research tool patenting and licensing (and its possible impact on innovation in health and agricultural research) may be effectively managed.

1. INTRODUCTION

Research tools are difficult to define precisely. They may be described, broadly, as any tangible or informational input required in the process of discovering a drug, a medical therapy, a diagnostic method, or a new crop variety. In short, anything that a researcher needs to use or access in the course of research—such as an assay, a genomic database, an animal model, crop germplasm and so on—may be classified as a research tool.[1] Research tools are defined by the U.S. National Institutes of Health (NIH) as the full range of resources that scientists use in the laboratory, including *"cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software."*[2] To this definition, one should add genes and gene fragments.

The classic statement on the possible consequences of protection by intellectual property (IP) rights of research tools in biomedical research was made by Heller and Eisenberg:

… the recent proliferation of intellectual property rights in biomedical research suggests a different tragedy, an "anticommons" in which people underuse scarce resources because too many owners can block each other. Privatization of biomedical research must be more carefully deployed to sustain both upstream research and downstream product development. Otherwise, more intellectual property rights may lead paradoxically to fewer useful products for improving human health.[3]

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Similar concerns have been expressed about agricultural research, for example by Boettiger and Bennett.[4]

2. RESEARCH TOOLS: KEY EVENTS

There are three key events of relevance to the global debate on the pros and cons of patenting research tools, all of which date from 1980, or thereabouts.

2.1 *Event one: the revolution in molecular biology*

The revolution in molecular biology has fostered the development of wholly new branches of scientific investigation, such as proteomics (the science of proteins expressed by genes), which has transformed the way research is conducted, as well as widened, enormously, the potential for scientific advances to address fundamental human problems in health and agriculture. Many of the immediate products of such research are intermediate or platform technologies of use to other researchers, but not (with certain exceptions such as diagnostic tests) final products capable of application by medical practitioners or farmers.

2.2 *Event two: the Chakrabarty case*

The landmark 1980 U.S. Supreme Court decision, *Diamond v. Chakrabarty*,[5] established that genetic inventions (in this case a genetically engineered bacterium capable of breaking down crude oil) were patentable subject matter under U.S. law. The application of the patent system in this way facilitated the development of a viable business model for the biotechnology industry. With the development of potentially revenue-earning products, often a long way off for many companies, they could nevertheless raise money, or realize value (for example, via licensing, assignment, or other forms of acquisition) through the patents taken out on research tools or other upstream genetic technologies.[6]

2.3 *Event three: the Bayh-Dole Act*

The 1980 Bayh-Dole Act amended the patent code in the United States, granting universities permission to patent inventions resulting from government-funded (federal) research, subject to government march-in rights. This was based on the premise that implementation of the Bayh-Dole Act would hasten innovation, facilitate the commercialization of research, and thereby move new and innovative products into the marketplace more quickly. As a result universities themselves have become key players in the development and patenting of new biotechnology inventions, most of which are in the nature of research tools rather than final products. Increasingly universities have developed extensive patent portfolios in both agricultural and biomedical technologies. Subsequently, most of the developed world has pursued similar policies to the United States in promoting the commercialization of the products of university research.

3. RESEARCH TOOLS: IMPLICATIONS AND CHALLENGES

The more technologically advanced developing countries, including Brazil, India and China, have in recent years pursued essentially similar policies to the United States in promoting the commercialization of the products of university research. But developing countries, even those with a relatively well-developed scientific and medical infrastructure, face very different circumstances from those in the United States and other developed countries. Although most developed countries have tried to emulate Bayh-Dole policies in different ways, the success of such policies in the United States owes much to institutional arrangements specific to the United States and is based on its unique higher education system and history of interactions between universities and businesses.[7]

An emphasis on patenting and licensing by universities as the chief means by which technology transfer occurs, as compared to publication and open knowledge sharing, may have negative implications for research in the area of public health or agriculture, as well as other areas. Since revenue prospects will be greater for products that would have a market in a developed country, this promise may further distort the allocation of research funding away from the specific public health problems of developing countries. Therefore, care must be taken to ensure that

research priorities, particularly those that could directly benefit poor people, are not distorted by the quest for larger licensing income.

Concerns about access to research tools apply both to the public and private sectors. In the public sector, for example, one university may wish to access the patented technology of another for research. Universities may wish to access private sector technologies, and vice versa. Private sector companies may experience difficulties in accessing each others' technologies.

Some see one university paying another to license a technology as perverse when most research in universities is publicly funded, even if the university is privately funded. But this is a logical consequence of introducing patenting into the university arena. In the United States, in the Supreme Court case *Madey v. Duke*,[8] the Court found that, since the "business" of Duke University was research and teaching, there was no exemption from patent infringement in its research, as the use of the patented invention was in furtherance of that business. The profit or nonprofit status of the user was not a critical factor for the court. Although not part of the court's judgment, the implication was that as universities were now enthusiastic users of patents and licenses, and litigated to enforce their patent rights, it would therefore be inconsistent for universities to seek exemptions for the use of third-party patented inventions for R&D in their own programs.

4. THE REALITY OF RESEARCH TOOLS

4.1 *Biomedical research*

In developed countries the evidence to date, which mainly comes from the United States, suggests that researchers in both the public and private sector have found various ways of coping with the new environment of patented research tools.

In biomedical research, working solutions include licensing, inventing around patents, infringement (often informally invoking a research exemption), developing and using public tools, and challenging patents in court. Changes in the institutional environment, such as the tightening of gene patenting rules introduced by the U.S. Patent and Trademark Office, and guidelines produced by NIH to encourage good patenting and licensing practices, appear to have further reduced the threat of breakdown and access restrictions, although the environment remains uncertain. It is clear, however, that these various working solutions involve costs in terms of either time or money or both.[9]

Furthermore, a recent study in the U.S. of researchers in academia, government and nonprofit organizations, and industry suggests that difficulties in gaining access to materials (for example, data or cell lines) through Material Transfer Agreements (MTAs) may have more significant implications for the conduct of research than patenting itself.[10]

A critical finding is that industry researchers experience significantly greater delays and difficulties in accessing proprietary technologies than academic researchers. In large part this is because industry researchers work, self-evidently, in a more commercial environment, are more patent aware than academics, and more liable to respect the patent rights of others and to assert their own rights with respect to their own proprietary technologies (including research tools). By contrast, while commercial activity and pressures have become much more widespread in academic circles, and patenting is common, researchers are less aware of patent issues, more likely not to check whether the technologies they use are protected, and less likely to assert their own rights against other academic researchers.

Another recent report from the Committee on IP Rights in Genomic and Protein Research and Innovation reached the following conclusion:

…the number of projects abandoned or delayed as a result of difficulties in technology access is reported to be small, as is the number of occasions in which investigators revise their protocols to avoid intellectual property issues or in which they pay high costs to obtain intellectual property. Thus, for the time being, it appears that access to patented inventions or information inputs into biomedical research rarely imposes a significant burden for biomedical researchers. For a number of reasons, however, the committee concluded that the patent landscape, which already is becoming complicated in areas such as gene expression and protein-protein interactions,

could become considerably more complex and burdensome over time.[11]

Accordingly the committee made recommendations that addressed "*an increasingly problematic environment for research in genomics and proteomics as more knowledge is created, more patent applications are filed, and more restrictions are placed on the availability of and access to information and resources*."

A special case is that of genetic diagnostic tests, which may be used either clinically or in the course of follow-on research. They, therefore, have a dual nature, both as a final product, and as a discovery tool. A survey of over 100 laboratories in the United States concluded that patenting and licensing practices in this field had had a negative impact on clinical use and the development of further genetic tests.[12]

These survey results relate to mainstream research of potential commercial value. Furthermore, it is likely that transaction costs could weigh more heavily on those working with limited resources on projects focusing on specific diseases particularly affecting developing countries. On the other hand, some public–private partnerships (for example, the Global Alliance for TB Drug Development) say that their philanthropic mandates can be useful in encouraging companies to license their IP more easily, and more cheaply, than would be likely in a wholly commercial exchange. It is, therefore, difficult to draw valid, general conclusions from the evidence currently available.

There is also very little empirical evidence of the impact of research tool patents in the biomedical field in developing countries themselves. More experience and empirical research are needed. The impact of such patents may be more significant in developing countries than in developed countries, as research institutions or companies in developing countries generally lack the legal and negotiating capacity to engage in complex negotiations and lack the organizational flexibility and funds to pay license fees, if required by patent holders.

4.2 *Agricultural research*

The institutional context for agricultural research, by which in this context we mainly mean crop research, differs from biomedical research. The size of the sector, and of the potential commercial market, is much smaller than in medicine. There is also a tradition of public sector institutes taking research right through to the point of commercialization (at least in traditional breeding programs), whereas in medicine commercialization is overwhelmingly a private sector activity.

The advent of biotechnology and the spread of gene patenting is one reason why the private sector in agricultural research has come to be dominated by a few large companies. In particular, the existence of a large number of overlapping patents for relatively important technologies has been a powerful incentive for merger and acquisitions, as well as strategic alliances. For example, patents on the Bt gene which can confer insect resistance on a wide range of different crops are strategically important for the whole industry. Controlling or denying access to strategic technologies is both commercially important to their owners and, correspondingly, liable to adversely affect research on crops where the commercial market is small (for example, subsistence crops in developing countries).

With respect to IP, research tools and agricultural research, a recent survey concluded that evidence:

…suggests that the effects on research of lack of access to needed technology have been more serious on average for biotechnologists working on agriculture than for those focused on human health. This might reflect the smaller set of promising technologies in agriculture and the lower level of resources available to help scientists surmount or invent around roadblocks. [13]

It also seems to be the case that patented genetic crop material (such as the Bt gene) is viewed as having more commercial value than many of the research tools used in biomedical research. Thus, whereas patent holders may disregard infringements in upstream biomedical research, or think it not cost effective to sue for infringement, in the case of more downstream agricultural research this may not be so.

5. ADDRESSING THE RESEARCH TOOLS CHALLENGE

Developing countries have a number of possible options, at the level of policy and practice, to address the possibility that proprietary restrictions will unduly limit the use of research tools. Possible approaches used or considered to address this issue include the following:

- changes in patenting policies
- research exemptions in patent law to reduce the risk of infringement in R&D
- compulsory licensing to allow access to upstream technologies
- institutional adaptations to facilitate access to needed technologies, such as guidelines intended to promote more appropriate behavior by participants in the system

5.1 *Patenting policies*

Countries may adopt different approaches to patenting. On the one hand, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) in Article 27 (1) obliges countries to grant patents across all fields of technology provided that the technology is new, involves an inventive step (or is *nonobvious,*) and is capable of industrial application (or is *useful*). On the other hand, the agreement allows various exclusions from patentability, such as discoveries of natural phenomena (which could include genes) that do not meet the patentability criteria.

Governments may choose whether or not to allow the patenting of genetic material. Plants and animals may be excluded from patentability, except for microorganisms, and nonbiological and microbiological processes. The TRIPS agreement does not specify how countries should define what an "invention" is, or how the criteria of patentability should be interpreted. Nor does it actually refer to genes, or genetic material, at any point.

The desirability of restricting patentability of genetic discoveries in this way will need to be assessed according to the circumstances of each country. For instance, countries that are mainly users of research tools patented abroad might promote the use of such tools by limiting their patentability. Other countries, with more advanced capacities in genomics, might favor a less-stringent interpretation of patentability but would need to be mindful of the possibility of restrictions on their widespread use.

If patents are granted, they can limit the scope of the claims to what has actually been invented. Patenting policy in biotechnology should aim to facilitate R&D of healthcare products and new agricultural crops. Unlike some other countries, France and Germany have introduced rules that limit the scope of patent protection for human gene sequences to the specific use disclosed in the patent application, thus excluding protection for future, as yet undiscovered, uses.[14] These rules were introduced because broad protection may disadvantage those wishing to build on the invention, while narrower claims may facilitate their downstream use.

5.2 *Research exemptions*

The TRIPS agreement allows the use of limited exemptions under Article 30, which has a possible application to the research tool issue as well as others:

Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.

In most of Europe, exemptions exist for acts performed privately, for purposes that are noncommercial, and for experimentation on the subject matter of the invention, even for commercial purposes.

In the United States, by contrast, there are no equivalent statutory exemptions, even for noncommercial or research uses. In the past, however, the courts have generally recognized some scope for *"making or using of a patented invention merely for experimental purposes, without any intent to derive profits or practical advantage… ."* In 2002, as noted above, the case of *Madey v. Duke* essentially ended this informal research exemption.[15]

There is an active debate in several countries about the appropriate scope of any research exemption. In 2004, the U.S. National Academies of Science (NAS) published a report on the U.S. patent system recommending that

the introduction of a formal research exemption for noncommercial purposes.[16] This recommendation was repeated in the subsequent report on genomic and proteomic research.[17]

Thus, there is a broad spectrum of ways in which the research exemptions allowed under the TRIPS agreement are implemented in different countries, and how these are interpreted by courts. The essential point, in this context, is how to ensure that follow-on research that may be important to innovation in the fields of health and agriculture is not inhibited. The appropriate scope of the research exemption must be considered in this light.

5.3 *Compulsory licensing*

In most countries, the law allows governments to issue compulsory licenses on a number of grounds, including in circumstances where the development of a research field of importance to public health or agriculture could be inhibited by the actions of particular patentees. For example, in the United Kingdom there are extensive powers in the Patent Act that, although rarely used, can remedy such situations. Section 48A (1) of the act, for instance, covers:

refusal of the proprietor of the patent to grant a licence or licences on reasonable terms … the exploitation … of any other patented invention which involves an important technical advance of considerable economic significance in relation to the invention for which the patent concerned was granted is prevented or hindered.

Similar provisions exist in many other countries. In the United States, the Patent Act does not provide for compulsory licensing as such, but there are similar march-in rights, as part of the Bayh-Dole amendments, only where federal funding of an invention is involved (Section 203).

In the European Union, the 1998 Biotechnology Directive, which has been implemented in national law by many member states, contains provisions that allow for compulsory licensing of patents or plant variety rights if prior negotiations with the owner are unsuccessful, provided that the resultant invention constitutes significant technical progress of considerable economic interest compared to the original invention claimed in the patent or plant variety right.

5.4 *Institutional adaptations*

Various initiatives have been considered or implemented to adapt or modify institutional practices around patenting and licensing.

One example of adaptation to the changing technical environment was the announcement in 2001 by the U.S. Patent Office of new guidelines on expressed sequence tags (short pieces of DNA that help to identify when particular genes are being expressed in cells). These guidelines tighten the specifications regarding what constitutes "utility," and provide guidance to patent examiners about how to apply the utility criterion to biotechnological inventions. In such cases, patentability can be established only if the patent application discloses a *specific*, *substantial* and *credible* utility.[18] It was intended that this new standard would prevent patents being granted on inventions for which only a speculative application is disclosed. The introduction of these tighter criteria may be one reason, among others, why patent applications in this area have declined recently.

Countries may also consider guidelines or other means to encourage or mandate patenting and licensing policies that promote innovation. In the United States, NIH, as the principal funder of academic biomedical research, took the lead in publishing in 1999 principles and guidelines on sharing biomedical research resources. These sought to promote the widest possible dissemination of research tools developed with NIH funds, in the interests of accelerating scientific discovery and facilitating product development. At the same time NIH considered that *"reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development."*[19]

In 2005, NIH introduced voluntary guidelines ("best practices") on the patenting and licensing of genetic inventions funded by NIH grants. On patenting, the guidelines said it should be considered whether:

…significant further research and development by the private sector is required to bring the

invention to practical and commercial application. Intellectual property protection should be sought when it is clear that private sector investment will be necessary to develop and make the invention widely available. By contrast, when significant further research and development investment is not required, such as with many research material and research tool technologies, best practices dictate that patent protection rarely should be sought.

On licensing, the guidelines provided a more extensive set of principles that support nonexclusive licensing as a general rule. Where exclusive licensing might be necessary to promote further development, the guidelines suggest that care should be taken to license only in the specific area where the licensee is working, to avoid blocking off other areas of research that may use the same technology. In addition, they said consideration should be given to including specific provisions to protect further research and public health. For instance, a license could reserve the right for the invention to be used in nonprofit research organizations for either research or educational uses.[20] Boettiger and Bennett argue that since the NIH guidelines appear to be working well, they should be applied across the board where federal funding is involved, keeping in mind, specifically, the situation in agricultural biotechnology.[21]

Guidelines on the licensing of genetic inventions have also been produced by the Organisation for Economic Co-operation and Development (OECD).[22] Apart from the text of the guidelines, an appendix contains a useful list of Web links to model agreements on various aspects of licensing and material transfers.

The international network of agricultural research centers, that is, the Consultative Group on International Agricultural Research (CGIAR), has a policy on IP, with the underlying principle to *"take every possible measure to facilitate access to research products for the public benefit, in particular in developing countries,"* while recognizing also that there will be exceptional circumstances when taking out patents may be necessary for the various centers to pursue their specific objectives.[23]

Some U.S. universities are indeed experimenting with new licensing arrangements. For instance, Stanford University proposes wording, along the following lines, as a standard means of establishing freedom for universities, public sector research organizations or, indeed, organizations such as public–private partnerships to be able to use particular technologies that it licenses exclusively to a third party:

Stanford retains the right, on behalf of itself and all other nonprofit academic research institutions, to practice the Licensed Patent and use Technology for any purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patent against any such institution. Stanford and any such other institution has the right to publish any information included in the Technology or a Licensed Patent.[24]

The organization Universities Allied for Essential Medicines has been set up in the United States to explore how universities can help ensure that biomedical end products, such as drugs, are made more accessible in poor countries, and to increase the amount of research conducted on neglected diseases, or those diseases predominantly affecting people who are too poor to constitute a market attractive to private sector R&D investment. The organization recognizes that university scientists are major contributors in the drug-development pipeline and that universities have an avowed commitment to advancing the public good.[25] The organization has developed a model equitable access license to further these aims.[26]

A body of technology managers called the Technology Managers for Global Health has been formed, as a subgroup within the influential Association of University Technology Managers in the United States, to press for similar sorts of arrangements to those promulgated by the Universities Allied for Essential Medicines and others. In conjunction with the Centre for the Management of Intellectual Property in Health Research and Development (MIHR), a co-sponsor of this *Handbook*, the Technology Managers for Global Health has published a booklet providing case studies of academic licensing to product

development partnerships for treatments for diseases affecting developing countries particularly.[27]

Another initiative seeks to draw on the success of the Open Source Initiative (OSI) which has developed a more or less proven research model, based on a general public license that makes modifications of a software program freely available to others to use or develop further. The important aspect of this approach is that it mobilizes innovative effort from a range of developers at little cost.

CAMBIA, a nonprofit organization based in Australia, both undertakes research in molecular biology in agriculture directed at the needs of developing countries and also seeks to overcome the problems of fragmented technologies by developing patent and technology databases and innovative licensing techniques that draw on the experience of OSI. CAMBIA has prepared a model license[28] that has the objective of creating a common pool within which improvements can be freely shared. On the other hand, the terms of this license may conflict with the existing licensing terms of other technologies, which should form part of the common pool.

The Public Intellectual Property Resource for Agriculture (PIPRA), the other co-sponsor of this *Handbook*, is an organization comprising universities, foundations, and nonprofit research institutions, which aims to make agricultural technologies more easily available for the development and distribution of subsistence crops for humanitarian purposes in the developing world. PIPRA seeks, through a variety of activities, including the compilation of patent and licensing databases, to mitigate problems arising from the fragmentation of proprietary technologies and materials among different institutions. It has also proposed a draft license to facilitate research relevant to developing countries.[29]

Another institutional approach is the potential use of patent pools. In 2000, a report by the U.S. Patent Office on patent pools and biotechnology patents concluded that the *"use of patent pools in the biotechnology field could serve the interests of both the public and private industry, a win-win situation*."[30] Among the benefits cited for this approach to licensing were: efficiency in obtaining rights to patented technology through one-stop licensing mechanisms; the distribution of risks associated with research and development; and the elimination of *blocking* patents or *stacking* licenses, and the consequent encouragement of cooperative efforts. Patent pools, therefore, could be most useful for technologies particularly relevant to developing countries, because the lack of strong market incentives may enable agreements that would otherwise be more difficult to engineer. Low-margin research directed toward problems of poor people might be promoted. Patent pools have also been proposed for the development of vaccines, which is appropriate given the large number of products owned by different entities and, consequently, the complexity of identifying, tracking, and obtaining licenses for patented technologies.

Patent pools have been established in the consumer electronics industry, specifically in relation to the broad adoption of industry standards. The biotechnology industry, however, is very different from the electronics industry. An OECD report noted:

…the pharmaceutical biotechnology industry may be fundamentally different from the electronics sector. It is not an industry in which defining standards is important, and assuring interoperability of technologies is not very important, especially not in the development of therapeutics. A company's worth is tightly tied to its intellectual property and fosters a "bunker mentality." There are likely to be disagreements among partners over the value of the different patents in a pool, and dominant players may not have a strong incentive to join the pool. If a limited field of application and essential patents can be defined, the patent pool model is worthy of consideration in biotechnology…[31]

The suitability of the patent pool for biotechnology patents certainly requires further study, as does the role of government in promoting them.

For these reasons, and others, patent pools in biotechnology have not developed as a response to fragmented patent ownership. In agricultural biotechnology in particular, cross-licensing and, ultimately, mergers and acquisitions are the common response.

6. CONCLUSIONS

While no specific guidance or conclusions can cover the specific circumstances of policy-makers, researchers, universities, research institutions, foundations or other organizations in given developed or developing countries, the several guidelines, enumerated below, might help to conceptualize a starting point within a broader framework:

- Developing countries need to consider implementing patent legislation, consistent with TRIPS, that meets their objectives, in particular with respect to genetic discoveries.
- Countries need to consider in their own legislation what form of research exemption might be appropriate, in their own circumstances, to foster research and innovation in health and agriculture.
- Countries should consider providing in their legislation powers to use compulsory licensing, in accordance with the TRIPS agreement, where this power might be useful as one of the means available to promote, inter alia, research that is directly relevant to the health and agriculture problems of developing countries.
- Countries should seek through patenting and licensing policies to maximize the availability of innovations, including research tools and platform technologies, for the development of products for human health and agriculture.
- Public funding bodies should introduce policies for sensible patenting and licensing practices, for technologies arising from their funding, to promote downstream innovation.
- Public research institutions and universities in developed countries should seriously consider initiatives designed to ensure that access to R&D outputs relevant to the health concerns of developing countries, and to products derived therefrom, are facilitated through appropriate licensing policies and practices. ■

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