6 The commercialization of new drugs and vaccines discovered in public sector research

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Introduction

Historically, there was a clear distinction between the roles of public sector research and corporate research in the discovery of new drugs and vaccines to solve unmet medical needs: public sector researchers, primarily funded by Government sources, performed the basic research and elucidated the underlying mechanisms and pathways of disease and identified promising points of intervention, while corporate researchers performed the applied research that discovered the drugs that would actually treat the diseases and then carried out the development activities to bring the drugs to market.

However, the boundaries between the roles of the public sector and the private sector in the discovery of new drugs have shifted significantly since the dawn of the biotechnology era in the mid-1970s. The public sector now has a much more direct role in the applied research part of drug discovery than is generally realized. This shift in roles has been attributed to changes in biological research that made the results of academic research immediately applicable to drug discovery fortuitously coinciding with changes in the legal framework governing the ownership, management and transfer of the intellectual property resulting from public sector research.

This chapter documents this fundamental change and presents a detailed compilation of public sector inventions that have resulted in new drugs and vaccines.

In a previous article,[9] we showed that over the past 30 years, 153[10] new Food and Drug Administration (FDA) approved vaccines, drugs and/or new indications for existing drugs were created during the course of research carried out in public sector institutions. These drugs consisted of 93 small molecule drugs, 36 biologics, 15 vaccines, eight in vivo diagnostics and one over-the-counter (OTC) drug. We identified the disease indications where public sector research had the highest impact – cancer and infectious diseases. We identified the research institutions that have been most productive in discovering new drugs. Finally, we showed that

drugs discovered by public sector researchers have had a disproportionately high therapeutic impact.

In this article we further analyze our dataset to identify the timelines of the development programs, from the start of the scientific program that led to the discovery, to the actual discovery of the drug, to the initiation of development and finally to FDA approval. We analyze the complex, multi-step development pathways that brought these discoveries to a successful conclusion with market introduction. We quantify the economic impact of these drugs, which vastly exceeds the Federal Government's annual investment in biomedical research.

Our study is limited to the US. Public sector research institutions (PSRIs) in countries such as the United Kingdom (UK), Israel, Canada, Germany, France, the Czech Republic, Belgium, Australia and Japan have also made significant contributions to new drug discovery, and we present preliminary data on their contributions.

Background

The relationship between academia and the pharmaceutical industry has gone through a number of cycles. Following the Pure Food and Drug Act of 1906 and the Food Drug and Cosmetic Act of 1938, it was the transfer of drugs discovered at academic institutions, such as thyroxine (University of Minnesota), insulin (University of Toronto), vitamin D and coumadin (University of Wisconsin), penicillin (University of Oxford), neomycin and streptomycin (Rutgers), methotrexate (M.D. Anderson Cancer Center), and others, that transformed the pharmaceutical industry from peddlers of bogus "patent medicines" to an ethical, research-based industry.

However, in the early 1960s, the Kennedy Administration started claiming rights to patents discovered in federal laboratories and at universities funded by federal grants. A principle was established that federally funded inventions would only be non-exclusively licensed. This substantially reduced the incentive for any company to make the pioneering investment needed to develop an early stage academic invention to the stage of market readiness because others could then piggy-back on their investment when the technology's viability had been demonstrated.

In the mid-1960s, three cases made industry even more reluctant to develop university inventions that had received federal funding:[11]

- The lawsuit between the University of Florida and Robert Cade over rights to Gatorade, where title to the patents was disputed and the National Institutes of Health (NIH) prohibited Cade from seeking US patents on his invention;
- The controversy over the cost increases caused by the exclusive licensing of the phenylketonuria (PKU) test invented at the University of Buffalo, which reached the floor of the Senate; and
- The Government taking title to patents on the cancer drug 5-fluorouracil and non-exclusively licensing the patents when federal funds were used to support

the initial clinical testing. The drug's discovery and pre-clinical development had been funded and technically supported by Hoffman-La Roche.

A 1968 US Government Accountability Office (GAO) study[12] found that no drug the Government owned the rights to had ever been developed and reached the public, and another 1968 study[13] by the Harbridge House consulting firm described projects as being "contaminated" by federal funding because of the constraints that federal ownership of the intellectual property brought with it.

By the late 1970s, Congress was generally concerned about a perceived loss of US industrial competitiveness to Europe and Japan. It was discovered that the Government owned 28,000 patents and had managed to license fewer than 4% of them, including fully paid up licenses and licenses from the Government to the inventor of his/her own patent.[14]

One of the responses to the 1968 GAO and Harbridge House reports had been the establishment of the Institutional Patent Agreement (IPA) mechanism for universities and non-profits to own and manage their own patents by Norman Latker at the Department of Health Education and Welfare. However, the Carter Administration halted the IPA process[15] and a number of universities and small business groups therefore lobbied for the passage of the Bayh-Dole Act[16] to allow universities, non-profit research institutes, teaching hospitals and small businesses to own the intellectual property resulting from federally funded research and to license it on terms of their choosing. The bill was finally passed in a lame duck session of the 96th Congress.[17]

Bayh-Dole was a relatively straightforward piece of legislation, requiring institutions to:

- Notify the funding agency of invention disclosures within two months of receipt and whether they intend to take title within two years;
- File patents on inventions they elect to own and not abandon them without giving the funding agency notice;
- Not assign title to third parties other than to patent management organizations;
- Include notice of the Government's rights in patent applications;
- On request, report on the utilization of their inventions to the funding agency;
- Share any income they receive with the inventors and use the remaining income only for research and education;
- Collaborate with commercial concerns to promote the utilization of inventions arising from Federal funding;
- Give licensing preference to small businesses in the US; and
- Ensure that their exclusive licensees substantially manufacture products in the US for sale in the US market.

In addition, the US Government retained a non-exclusive license to practice the patent throughout the world and the right to "march-in" and grant additional licenses in the public interest if the invention was not being brought to practical application or meeting public health and safety needs.

Institutions were allowed to grant exclusive licenses for five years; the five-year limitation was removed four years later in an amendment to the Act.[18]

The Bayh-Dole Act provided no new funding and so did not require periodic reauthorization, which would have provided opportunities for Congress to amend the Act. The Act has therefore been in place for almost 30 years, with only one major amendment, in 1984.

The Stevenson-Wydler Technology Innovation Act of 1980[19] and the Federal Technology Transfer Act of 1986[20] established the foundation for technology transfer for Federal Government laboratories. Like their Bayh-Dole counterpart, these laws recognized the need for enhanced commercial dissemination of technologies from publicly funded research to private industry, establishing analogous mechanisms for laboratories of the US Government. For the first time, federal laboratories were required to grant licenses for commercial development of technologies invented in their laboratories and were incentivized to do so by being able to keep the proceeds within the laboratory. Inventors were given a share of the royalty income and laboratories were permitted to keep the remainder of the funds to support the cost of technology transfer and to further their research and training missions.

The Federal Technology Transfer Act also enabled federal laboratories to take a more active role in cooperating with companies developing technologies through Cooperative Research and Development Agreements (CRADAs). Some of the technologies licensed by the NIH were discovered as CRADA inventions, such as a method of administering Taxol, or were further developed under the CRADA mechanism with the licensee, such as Havrix, the first hepatitis A vaccine.

The historic roles of public sector and corporate research in drug discovery

Historically, there was believed to be a clear distinction between the roles of public sector and corporate research in the discovery of new drugs and vaccines to solve unmet medical needs. Although drug discovery occasionally is serendipitous, such as when the ability of sildenafil (Viagra) to treat male erectile dysfunction was observed as a side effect in an unsuccessful trial of sildenafil to treat angina, modern drug discovery is hypothesis driven and generally uses one of two scientific approaches:

- High throughput screening of large numbers of compounds against an assay to identify compounds that bind to a molecular target of interest; or
- Rational drug design based on detailed structural information about the molecular target of interest.

Traditionally, the role of public sector researchers, primarily funded by Government sources, was to perform basic research and elucidate the underlying mechanisms and pathways of disease and identify the molecular targets that would provide promising points of intervention in the etiology of the disease. Corporate researchers would then take the results of this basic research and carry out the applied research that discovered the actual drugs that would modulate the

targets and treat the disease. The public sector basic research findings were transferred to industry at arm's length, via publications in the scientific literature and presentations at scientific conferences. They were available to all.

In the applied phase of the research, patents are applied for that will protect the investment the company will need to make in developing the product and bring it to market, and the knowledge can be localized to a single company.

An excellent example of this traditional, arms length paradigm was Julius Axelrod's Nobel Prize winning research at the NIH elucidating the basic mechanisms of neurotransmitters,[21] which provided the foundation for the pharmaceutical industry to discover an entirely new class of drugs, the selective serotonin reuptake inhibitors (SSRIs) such as Prozac, Paxil and Zoloft that have been immensely important in the treatment of depression and have also been extremely successful commercially.

There seems to be little dispute about the extent of the contribution of public sector basic research to drug discovery under this paradigm. Studies by Cockburn and Henderson[22] showed the complex inter-relationships between public and private research in the pharmaceutical industry. Zycher, DiMasi et al.[23] have shown that upwards of 80% of drugs are based on basic scientific discoveries made in the public sector, while Toole[24] has identified the complementary nature of public and private research in drug discovery. He summarized the research on the role of public sector basic research as follows:

> Most of this research highlights the role that basic research plays in opening new avenues to therapeutic outcomes. It is useful to think of the new therapies pursued by industry scientists as therapeutic jigsaw puzzles that must be completed before any new drug treatment can be brought to market. Public basic research provides either completely new puzzles or resurrects puzzles that were believed to be unsolvable. In either situation, almost all the case studies characterize the new puzzles emerging from public basic research as embryonic. *These puzzles are often in their earliest stages of scientific development and may embody only the faintest outline of a promising new therapy.* A key finding from these studies is that public basic research is characterized by a high degree of uncertainty in both its scientific maturity and its potential market applicability. Beyond supplying new ideas for therapies, public basic research can contribute to industry solutions by providing pieces of the puzzle or *by providing the clues required for discovering new pieces*. In the case studies, these pieces and clues take the form of methods for identification of target compounds, validation of these targets, methods for producing sufficient quantities of the compound for animal and human testing, and the design of laboratory models for animal studies. Because of the complexity and diversity of the puzzles confronting industry scientists, the pieces drawn from public basic research are rarely the "plug and play" variety. Information from this research must be shaped to fit the specific puzzle under investigation. Moreover, when public basic research only provides clues, new pieces must be invented to fit the puzzle (citations omitted; emphasis added).

Marcia Angell[25] quotes studies which showed that around 85% of the basic scientific research that led to the discovery of new drugs came from sources other than the drug industry. However, Angell is wrong when she states:

> And so on and so on. There is no question that publicly funded medical research – not the industry itself – is by far the major source of innovative drugs.

The studies she had just cited ~~have~~ shown that publicly funded medical research is the major source of the scientific leads that ~~pointed~~ to how innovative drugs could be discovered. These studies did not identify the actual drugs themselves.

Toole[26] discovered a quantifiable correlation between investment in publicly funded basic research and corporately funded applied research. He found that a 1% increase in the stock of public basic research led to a 1.8% increase in the number of successful NME applications after a lag of about 17 years. He further estimated that the total direct return to public basic research was 43% – i.e., a $1 increase in investment in public sector basic research yielded about $0.43 in annual benefits in NME innovation in perpetuity.

However, working in the technology transfer profession for many years, we observed that the boundaries between the roles of the public sector and the private sector in the discovery of new drugs had shifted significantly since the dawn of the biotechnology era. We saw that PSRIs were playing a much more important role in drug discovery than had previously been identified and documented and were having a significant role in the applied research phase of the drug discovery process, identifying the new drugs themselves and creating some, or all, of the intellectual protecting these new drugs. The primary objective of this study is therefore to document the extent of this new role for the public sector in the applied phase of the research and therefore in the creation of IP protecting the commercialized products.

~~This~~ emergence of this new paradigm has been attributed to changes in biological research that made the results of academic research immediately applicable to drug discovery fortuitously coinciding with the establishment of the legal framework which governs public sector technology transfer described in the previous section.[27] Under this new paradigm, the results of public sector scientific research, in addition to being freely published in the scientific literature, can, to the extent they meet the criteria of novelty, utility and non-obviousness to constitute a patentable invention, be converted into intellectual property and then be transferred through commercial license agreements to a companies for further development.

Particularly in the life sciences, academic scientists have embraced this new paradigm. Murray[28] analyzed three years worth of articles in *Nature Biotechnology* from 1997 to 1999 and found that there was a corresponding issued US patent on just under 50% of the discoveries being reported, a phenomenon she termed the "patent-paper pair".[29] As Murray acknowledged, the discoveries submitted to *Nature Biotechnology* probably self select for those with commercial relevance,

so the 50% figure she found may be higher than what would be found for the overall scientific literature. Lebovitz[30] examined the life science publications in *Science and Nature* in a six month period and found that 32.7% of the biomedical research articles surveyed in the study were associated with underlying patent applications, 17.9% directly covering the research disclosed in the scientific publication, and 11.7% related to an enabling technology that was utilized in the research.

Under the new paradigm that we are evaluating, we consider that a PSRI plays a role in the applied phase of drug discovery research if it, solely or jointly creates *product-specific* intellectual property pertaining to the drug that ~~was~~ transferred to a company through a commercial license. In most cases, the intellectual property is a patent or patent application. However, a few products have used proprietary biological materials developed and licensed by the institution. For example, MedImmune licensed proprietary strains of influenza virus developed by Dr. Hunein Maassab at the University of Michigan to develop FluMist, and FluMist is therefore included in our study.* Similarly the strain of *M. tuberculosis* used in the BCG vaccine and the trademark on the name "Tice" are owned by the University of Illinois and are licensed by them to the manufacturer, OrganonTeknica.

In this study we use the term "public sector research institute" ~~(PSRI)~~ in its broadest sense to include universities, research hospitals, not-for-profit research institutes and federal laboratories.

We use the term "drug" to refer to any product that received marketing approval from either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) of the ~~US Food and Drug Administration (~~FDA~~)~~. We therefore include small molecule drugs, protein-based biologics, vaccines and *in vivo* diagnostics approved since 1970. Products that have received regulatory approval only outside the US are not included in this study.

There are multiple layers of patents protecting a particular drug. In this study, we classified patents into six categories.

We read all the independent claims of the 531 public sector, joint and company patents that we identified and classified the claims into the following categories:

> **Screening:** Claims a way of detecting the existence of a condition or compound either in vitro or in vivo, and of identifying a molecule that is pharmacologically active against the condition.
>
> **Method of synthesis:** Claims a specific way of making a compound or class of compounds, but does not cover the composition of matter of the pharmacologically active constituent of the marketed drug.

* The University of Michigan has since received a U.S. patent on the strain used in FluMist.

Composition of matter: Claims the pharmacologically active molecule, or family of molecules, contained in the marketed drug, including peptides and proteins and the specific DNA sequences used to produce them.

Method of treating: Claims a way of treating a specific condition using the pharmacologically active molecule.

Formulation: Claims a way of delivering a compound, or a way or preparing a pharmacologically effective combination of compounds, but not the composition of matter of the pharmacologically active ingredient compounds which make up the combination.

Medical device: Claims an instrument or apparatus which does not achieve its primary intended purposes through chemical action and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

We analyzed the patents as follows.

An individual patent frequently contained more than one type of claim, most often a composition of matter and a method of treating. Each patent was given a score of 1 in each category in which it had at least one independent claim. For example, if there were two PSRI patents protecting a drug, and one only had three independent composition of matter claims and the second had one composition of matter independent claim and two method of treating independent claims, it would have been given a score of two in the composition of matter category and one in the method of treating category

While the objective of our research was to comprehensively identify the public sector intellectual property underlying these drugs, including intellectual property jointly owned with a company, it was not one of our objectives to make a comprehensive identification of all the company owned intellectual property protecting the drugs. Our primary source for company owned intellectual property was the Orange Book, and so is most complete for small molecule drugs, including *in vivo* diagnostics, and is less complete for biologics and vaccines. The results are shown in Table 6.1.

For the PSRI solely owned patents, there were an average of 2.5 patents protecting each drug, and these patents had an average of 1.5 types of claim per drug. The most common types of claims were composition of matter which were found for 56% of the drugs, followed by methods of treating, found for 52%. Methods of screening patents were only found in 5% of the drugs and formulation patents in 10% of the cases.

We therefore use the term "discovered in whole or in part" through public sector research throughout the study.

Table 6.1 Types of patent claims protecting drugs

Patent ownership	*PSRI*		*Joint PSRI & company*		*Company*	
No. of drugs with patents	133		17		56	
No. of patents	329		45		157	
Average patents/drug	2.5		2.6		2.8	
No. of drugs with claims for:						
Screening	8	6.0%	2	11.8%	1	1.8%
Method of synthesis	38	28.6%	1	5.9%	10	17.9%
Composition of matter	85	63.9%	8	47.1%	43	76.8%
Method of treating	80	60.2%	13	76.5%	31	55.4%
Formulation	17	12.8%			9	16.1%
Medical device	2	1.5%				
Average types/drug	1.7		1.4		1.7	

Examples of the types of the different extents of the contributions of PSRIs to the discovery of specific drugs are as follows.

- In the case of Cialis, Cold Spring Harbor developed the screening technology and licensed it to ICOS Corporation, which used the tools to discover the actual active molecule, tadalafil, which it then took through clinical development. Cold Spring Harbor therefore does not receive royalties on sales of Cialis.
- In the case of Serafem, MIT showed that selective serotonin reuptake inhibitors such as fluoxetine hydrochloride, the active ingredient in Prozac, were effective in treating premenstrual dysphoric disorder and licensed it to Eli Lilly who had already carried out the safety and efficacy studies to secure FDA approval to market Prozac as an anti-depressant.
- In the case of ReoPro, SUNY isolated the 7E3 murine antibody that binds to fibrinogen to inhibit clotting and licensed it to Centocor. Centocor chimerized the antibody, creating abciximab. The clinical development was carried out by Lilly.
- In the case of Neupogen, Memorial Sloan Kettering cloned the gene for G-CSF and based on G-CSF's efficacy in regenerating neutrophils. Amgen's role was to develop the producing cell line and take the compound through clinical development.
- In the case of Taxol, Dr. Robert Horton, a chemist at Florida State University invented the semi-synthetic process for manufacturing Taxol from an extract of pine needles. This innovation freed Taxol from its dependency on the rare and slow growing Pacific yew tree as its sole raw material source and allowed Taxol to become a $1.6 billion dollar drug in its peak year of sales. Florida State licensed the process to Bristol-Myers, who had licensed the NIH's extensive clinical data on Taxol and method of administration to patients.

- In the case of Geodon, the University of Kansas discovered the use of cyclodextrins as a delivery agent for drugs and licensed them to CyDex, which partnered with Pfizer to formulate ziprasidone mesylate to treat schizophrenia. Pfizer carried out the clinical development.

In the case of biologics, there is frequently a layer of patents covering genetic engineering platform technologies that are needed to create and/or manufacture the drugs. Many of these platform technologies were created and are owned by PSRIs and are discussed in more detail below. If the only public sector contribution to a specific drug was through one of these platform technologies, we did not include that drug in our study, because the public sector did not contribute to the discovery of the specific, marketed product.

With the exception of the exclusion of such platform technologies, we deliberately use the term "discovery" very broadly, to refer to any intellectual property that protects the identification, composition of matter, method of treating, manufacture or formulation of a drug which was licensed by the PSRI to the corporate developer of the technology.

A broad range of contractual relationships between the public and private sectors is encompassed in our study. In some cases, such as Neupogen discussed above, the PSRI made the complete discovery itself and subsequently licensed the invention to the developing company. In other cases the relationship started with a collaboration between a public sector institution and a corporate collaborator, resulting in initial patents being jointly owned. In these circumstances, the corporate partner generally obtains a license to the PSRI's undivided interest in the patents. Other cases involved simultaneous inventions in the public and private sectors, resulting in interference proceedings, which were sometimes resolved through negotiation rather than through the patent office. Massachusetts General Hospital's interest in the arthritis drug Enbrel came through a license agreement structured to take into account a negative outcome should an interference be declared.[31] And finally, in a few cases, the developing company did not feel it needed a license to the public sector intellectual property, leading to litigation which resulted in a license being judicially imposed.

There are instances of academic research resulting in valuable drugs where the institution did not apply for a patent, to their considerable financial cost (although the public still benefitted from the product becoming available to them). These generally involved a new use for an existing drug, where there was adequate intellectual property protection available to protect the development of the drug for its original intended indication. For example:

- In the late 1950s, Dr. Gregory Pincus at the Worcester Foundation for Experimental Biology discovered that synthetic progesterones were effective female contraceptives. Pharmaceutical companies such as Syntex and G.D. Searle were only developing synthetic progesterones to treat menstrual irregularities, so Pincus' discovery would have been patentable as a new method of treating patent, but he failed to apply for a patent and therefore was

unable to license his discovery; the contraceptive pill is therefore not included in our study. G.D. Searle, which marketed the drug, made some gifts to the Worcester Foundation, but the Foundation was ultimately absorbed into the University of Massachusetts in 1997.

- More recently, Dr. Lawrence Jacobs, Chair of the Neurology Department at the University of Buffalo Medical School, carried out the key clinical trial, funded by NIH, that showed the efficacy of intramuscular beta-interferon 1a in the treatment of multiple sclerosis. Biogen agreed to support the trial with their version of beta interferon 1a. Multiple sclerosis turned out to be the only major clinical use of beta-interferon 1a, which was the first product to which Biogen had retained development rights and which became its first clinical product under the trade name Avonex. Biogen subsequently gave the University of Buffalo $1.5 million to endow the Irvin and Rosemary Smith Chair in Neurology in the School of Medicine and Biomedical Sciences, which Jacob held until his death from cancer in 2002, considerably less than Buffalo would have received had they secured a patent on the new use of interferon 1a and licensed it to Biogen.

Avonex is in fact included in our study, not because of Jacobs' work, but because it was determined in litigation that Avonex infringed one of the Ringold patents jointly owned by Stanford University and Berlex,

As noted above, our study does not include the role of public sector research in developing the platform technologies discussed above that have contributed to the development of new classes of biological drugs. Such platforms include:

- The discovery of recombinant DNA technology at the University of California, San Francisco and Stanford University ("Cohen-Boyer");
- The discovery of bacterial production methods for recombinant DNA by the City of Hope Medical Center ("Riggs-Itakura");
- The discovery of production methodologies and chimerization techniques for antibodies at City of Hope Medical Center and Genentech ("Cabilly");
- The discovery of methods to produce glycosylated recombinant proteins in mammalian cells at Columbia University ("Axel");
- The discovery of methods to generate functional monoclonal antibodies at Columbia and Stanford ("Morrison-Herzenberg");
- The discovery of PEGylation techniques to extend the serum half-life of protein drugs at the University of Alabama Huntsville ("Harris"); and
- The discovery of siRNA methods of gene silencing at the University of Massachusetts and the Carnegie Institution, which was awarded the Nobel Prize in Physiology and Medicine in 2006 ("Mello-Fire").

These platform technologies have enabled very large numbers of products – essentially every genetically engineered product ever approved – and have been broadly licensed non-exclusively. Despite being licensed at relatively modest royalty rates, they have resulted in enormous royalty streams because of the

multiple products covered and so have been among the most valuable academic patents ever issued.

- The Cohen-Boyer patents generated over $254 million in income before their December 1997 expiration.
- In 2002 a jury awarded City of Hope $300 million in damages in addition to the substantial royalties City of Hope had already received from Genentech for Riggs-Itakura.
- Cabilly generated $250 million in 2007 alone for Genentech, the exclusive licensee of City of Hope's interest (with City of Hope receiving approximately 38% according to Genentech's 2007 10K).
- The Axel patents are estimated to have generated $790 million before their 2000 expiration.
- Stanford describes its interest in the Morrison-Herzenberg patents as currently being its biggest royalty generator.

Nonetheless, we did not include these products in our study because the platforms did not contribute to the discovery of specific individual drugs.

Finally, we did not include nutritional products which did not require FDA approval, though even here public sector research has sometimes played a role. For instance, Caltrate was discovered by the University of Texas Southwest Medical Center, while Caltrate Colon Plus was discovered at Dartmouth.

Disease pathway based intellectual property

There have been a few attempts to combine the old paradigm with the new when academic institutions which had identified new disease pathways attempted to obtain patents on any drug which modulates the pathway.

The first and best-known example was when the University of Rochester received US Patent 6,048,850 titled "Method of inhibiting prostaglandin synthesis in a human host". The patent was issued on April 11, 2000 with claims to all methods of inhibiting prostaglandin H synthase-2 (PGHS-2, more commonly called COX-2), and the next day Rochester sued G.D. Searle, manufacturer of the first COX-2 inhibitor, Celebrex, claiming infringement. After a herculean fight on which the university reportedly spent tens of millions of dollars, culminating in an unsuccessful appeal to the Supreme Court, the patent was invalidated for lack of enablement.

The next case started when US Patent 6,410,516 "Nuclear factors associated with transcriptional regulation" was issued on June 25, 2002 to the President and Fellows of Harvard College, Massachusetts Institute of Technology and the Whitehead Institute for Biomedical Research, claiming all methods of inhibiting expression of a gene whose transcription is regulated by NF-κB by reducing NF-κB activity in that cell. The patent was exclusively licensed to ARIAD Pharmaceuticals, who sued Eli Lilly asserting that their osteoporosis drug Evista and sepsis drug Xigris infringed the patent. ARIAD won at the District Court level

and was awarded $65.3 mm in damages,[32] but the patent was invalidated for lack of written enablement by the Court of Appeals for the Federal Circuit (CAFC)[33,34] a decision which was reaffirmed at a rehearing *en banc*.[35] In the interim, Amgen filed suit against ARIAD to invalidate the patent and certify that its blockbuster arthritis drug Enbrel, and a second arthritis treatment, Kineret, did not infringe the patent. In September 2008, a federal judge in the US District Court of Delaware granted Amgen's motion for summary judgment of non-infringement of seven claims,[36] and in June 2009, the CAFC affirmed this decision.[37]

Lest it be thought that this degree of patent over-reaching is a purely academic phenomenon, in an interesting (and some might say hypocritical twist in view of the outrage they had expressed over the Rochester case) Pfizer (who had bought G.D. Searle), did precisely the same thing. Claim 24 of US Patent 6,469,012 "Pyrazolopyrimidinones for the treatment of impotence", issued on October 22, 2002 to Pfizer, Inc. was:

> 24. A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a selective cGMP PDE.sub.v inhibitor, or a pharmaceutically acceptable salt thereof, of a pharmaceutical composition containing either entity

and claimed all methods of treating male erectile dysfunction by administering a selective cGMP PDE-5 inhibitor. Immediately upon allowance of the patent, Pfizer sued Bayer and GlaxoSmithKline for their drug Levitra and Eli Lilly and their partner ICOS Corporation for their drug Cialis. Glaxo, Bayer and Pfizer entered into an agreement on a worldwide basis to settle the patent infringement and nullity proceedings.[38,39] The Lilly lawsuit was suspended while the US Patent and Trademark Office (USPTO) reexamined Pfizer's method-of-use claim and invalidated it on the basis that certain prior art rendered the claimed invention not new, and therefore unpatentable under 35 USC §102(b), and obvious and unpatentable under the doctrine of obviousness-type double patenting. The Board of Appeals and Interferences declared the patent invalid in February 2010.[40]

That said, it is possible to license drug discovery pathways on a collaborative basis, including know-how as well as patents. For example the erectile dysfunction drug Cialis discussed above was developed from a class of PDE molecules discovered using a yeast screen containing human genes invented and patented by Cold Spring Harbor Laboratory and licensed to ICOS at its formation in 1990. Cold Spring Harbor suggested the class of molecules to ICOS which then isolated the actual active compound, tadalafil, and confirmed its potential for treating erectile dysfunction. Cold Spring Harbor received 125,000 shares of ICOS stock, which was worth a considerable amount when ICOS' stock soared after its 1991 Initial Public Offering (IPO), but Cold Spring Harbor does not receive royalties on sales of Cialis since its patents do not cover the product tadalafil itself[41]. Cialis is therefore included in our study. Lilly bought ICOS for $2.6 billion in 2006.

Methodology

This study uses the same dataset that was used in the NEJM article referenced in the Abstract. This section provides a fuller account of the methodology than the word limits of the NEJM allowed.

There has been no systematic collection of outcomes of individual transfers of technologies invented by public sector researchers. Since 1991, the Association of University Technology Managers (AUTM) has conducted an Annual Licensing Survey[42] which provides aggregate statistics on the outcomes of academic institutions' technology transfer activities, but the specific technologies, their licensees and the success or failure of the licensees' development efforts are not identified.

Issued US patents have always been a matter of public record once they are issued and, since November 2001, US patent applications have been published 18 months after filing[29],[43] and are therefore also a matter of public record. Universities receive substantial numbers of patents, but again, patents contain no indication of whether a product covered by that patent ultimately reached the market.

Frequently, public sector technologies are licensed to small, privately owned companies that have no obligation of public disclosure of their financial status, business plans or partnerships. Nonetheless, such companies frequently make voluntary, though generally limited, disclosures about their activities. However, if the company files for an IPO, which is highly likely if the company is successful in developing a drug and partnering it with a large company, it will be required to make substantial disclosures to the Securities and Exchange Commission (SEC) about its business activities, including the technologies it has licensed and the financial terms of those licenses. These disclosures provide one area of systematic investigation.

Recombinant Capital,[44] a consulting company now owned by Thomson Reuters, has systematically collected license agreements filed by biotechnology companies with the SEC since the earliest days of the biotechnology industry. Their databases, ReCap.com and rDNA.com, contain details of both the companies' in-licensing of technologies from universities, as well as their out-licensing of the same projects to larger companies after they have been advanced towards market entry. A search of this database with the keyword "university" yields over 1,000 hits. Again, however, this database contains no indication as to whether the technology was ultimately successful and resulted in a marketed product.

We therefore created a comprehensive database of successful drug discovery and development projects that owe their origin, at least in part, to inventions resulting from research carried out in the public sector.

Companies, whether large or small, are rarely motivated to publicly acknowledge that their key intellectual property was obtained from others. Rather, they prefer to promote their in-house technical capabilities and prowess to their investors. The first (and most difficult) step in our research was therefore to identify which drugs resulted from public sector research. We obtained this information from a diverse array of sources, as follows.

- The FDA's Orange Book contains details of certain of the patents protecting drugs that have received approval under New Drug Applications (NDAs) but not Biologics License Applications (BLAs). The Orange Book only lists patents still in effect, and only lists composition of matter, method of treating and formulation patents.
- A newer database created by Recombinant Capital, ReCap IP, contains the information from the Orange Book and links the patents listed in the Orange Book with information from the USPTO database, such as the assignee of the patents. One or more of the patents being assigned to a PSRI is *prima facie* evidence that there is a license to technology owned by that institution.
- A number of AUTM sources were useful:

  - In 1994 and 1996, AUTM conducted Public Benefits Surveys[45] which identified a number of products that had reached the market based on licenses from universities, including a number of drugs.
  - Since 1997, the AUTM Annual Licensing Survey has included a series of Vignettes of individual transactions that have been self-reported by the institution. Some of these described successful drug discovery projects.
  - In 2005 AUTM started a systematic (but still voluntary) collection of success stories. These have been compiled in a database[46] currently containing 1,620 entries which are the bases for AUTM's "Better World Report" publications in 2006, 2007, 2008 and 2009. The biotechnology, health sciences and pharmaceuticals sections contain almost 140 stories and those that pertained to a marketed drug were added to our database.
  - As discussed earlier, the AUTM Annual Licensing Survey collects detailed statistics on various measures of technology transfer activity and performance at the level of individual institutions but does not identify specific transactions and outcomes. However, one of the metrics reported to the Survey is royalty income, and those institutions that have substantial royalty income frequently owe this to a marketed drug. We identified institutions with high royalty income and attempted to identify which owed their high income to marketed drugs, by browsing the institution's website, Google searches, etc.
  - The University of Virginia Patent Foundation has assembled a substantial number of success stories of academic licensing, and published them on its website.[47] Those that pertain to drug discovery were included in our study.
  - The NIH has identified and documented the drugs and vaccines that have resulted from licensing of inventions made in its intramural research program, that is, research conducted in Government laboratories at the NIH.[48]
  - The NIH's iEdison invention reporting system has a page listing a number of drugs discovered with funding from the NIH's extramural research program.[49]

- A number of academic drug discoveries have led to litigation that revealed the role of the academic institution in the discovery of the drug. Publicly available information, such as the Complaints, Opinions, news stories and so forth, contain useful information.
- Academic institutions with substantial royalty incomes sometimes monetize the royalty stream by selling the right to receive the royalties to a third party. Sometimes the inventors ~~have sold~~ their portion of the royalty stream independently of the academic institution. The specialized financial firms[50] that organize these transactions frequently make public announcements of the completion of these transactions and these revealed some public sector ownerships of which we were not previously aware.
- Finally, serendipity played a part – e.g., a front page story in the *Wall Street Journal*[51] about the roles of Duke and Genzyme in the development of Myozyme to treat Pombe disease resulted in Myozyme being added to the database; preparing a *Harvard Business School* case study on AngioMax and The Medicines Company[52] for a course on the management of innovation identified that AngioMax was the result of a collaboration between Biogen and the Wadsworth Center of the New York State Department of Health.

As a quality control measure, in the middle of May 2009, we emailed the list of products and discovering institutions that we had discovered as of that date to the list of technology transfer office (TTO) directors maintained by AUTM and asked for omissions and corrections. This step resulted in nine new products being brought to our attention.

The second step in our research was to determine the patents protecting each product. Our primary source of data here was the USPTO database.[53] Some of these patents were identified in the normal course of identifying that a particular drug should be included in our database. In order to gather as comprehensive a list of the underlying patents as possible, we searched FDA drug labels,[54] ReCapIP, and conducted internet searches, which would yield hits such as FDA patent term extension dockets or marketing websites dedicated to a particular drug. We further browsed the Federal Register for FDA patent term extension notices.[55] The browse products capability of ReCapIP was especially helpful because the primary view contains all underlying patents in the ReCapIP system, along with the corresponding assignee, without the user having to drill down further for that information. This allowed us to search through all of the products in the ReCapIP database methodically and efficiently to identify related public sector patents. Although the initial objective of this search was to identify patents protecting drugs already in our database, it yielded about 15 further drugs for inclusion in our study. The study by Sampat[56] using older versions of the Orange Book identified an additional nine drugs where the public sector patents had expired and these have been included.

The third step in our research was to determine as much as possible about how each drug was developed. The rDNA database allowed us to trace the

various corporate transactions that drugs passed through on their way from discovery to market as they were licensed, acquired and divested from one company to another.

The fourth step in our research was to obtain information on the drug's approval process from the FDA's drug and biologic approval databases.

Using data from these primary sources, together with Internet searching, which frequently found articles that told the story of how the transition from bench-to-bedside had been brought about, we attempted to identify for each product:

- The Principal Investigator(s)/Lead Inventor(s) and his/her institution(s);
- The funding sources and dates of any federal grants;[57]
- The date of the earliest patent application cited in the issued patents;
- The date of issuance of the first patent covering the drug;
- The identity of the initial licensee and the date and terms of the license;
- The date, nature and value of any transactions by the initial licensee and subsequent sublicensees or assignees during the course of bringing the product to market, subdivided into those occurring before and those occurring after FDA approval;
- The dates of FDA approval of all the NDAs and BLAs incorporating that active ingredient;
- For drugs receiving NDA approval, the FDA chemical classification, whether the product received standard or priority review and whether it received orphan drug designation; and
- US sales of the product.

The cutoff date for our data collection was September 1, 2009 for drugs to have received FDA approval.

Results

Summary of the results in the prior article

The following are the findings that were published in the article in the *New England Journal of Medicine* referenced in the abstract earlier.

- 153[58] FDA approved drugs were discovered in whole or in part at US public sector institutions[59], including:
  - 102 NMEs (including eight *in vivo* diagnostics and one OTC product);
  - 36 biologic drugs; and
  - 15 vaccines.
- The NMEs approved from 1990–2007 represented:
  - 9.3% of all NDAs in this time period; and
  - 21.1% of NMEs receiving Priority Review.
- The 153 drugs fell in 16 therapeutic categories; Oncology and Infectious diseases were 50% of the total.

- The 153 drugs were discovered or co-discovered by 75 PSRIs;
  - 22 by the NIH;
  - 11 by the University of California System;
  - 8 by Memorial Sloan-Kettering Cancer Center;
  - 7 by Emory University;
  - 6 by Yale University.

The identities of the 153 products are contained in Table 1 in the Supplementary Appendix to the NEJM article.

The translational process

In the balance of this chapter, we focus on the process by which the discovery made in the course of PSRI research was translated to the marketplace.

Initial developing company

We classified companies that were the initial licensee for the products into the three categories used by AUTM in its Annual Licensing Survey:

- Large company – a company with more than 500 employees
- Small company – a company with fewer than 500 employees
- Spin-out – a company formed specifically to develop the technology, a special case of a small company.

The distribution of licensees between these three categories is shown in Table 6.2. We classified the company according to its status *when the license was executed*. For instance, today Amgen is clearly a large company, with over 20,000 employees worldwide. However, when Amgen licensed Neupogen from Memorial-Sloan Kettering in 1986, it was a small company and is so classified in our study. Neupogen was one of the two products that propelled Amgen's growth.[60]

Some 92 different companies initially received licenses to the PSRI discoveries. Small companies (including the category of spin-out companies which were specifically founded to develop the drug) constituted 57.5% of the companies which initiated development of the drug.[61] The percentage of licenses with large companies we found, 42.5%, is a little higher than that typically reported in the

Table 6.2 Types of companies that initiated development of PSRI invented drugs

Type of entity	*Number*	*%*
Large entity	65	42.5%
Small entity	65	42.5%
Start-up	23	15.0%
Total	153	

AUTM Annual Survey, where the percentage of licenses with large companies was 35.1% in 2008. Since the AUTM Survey includes all types of technologies, it is possible that the difference is the result of life sciences inventions being more likely to be licensed by large companies due to the high costs and commercial demands to bring such products to market.

Marketing company

When the licensee is a large company, they generally have the resources to take the product to market. Our study confirmed that this is generally the case, though in a few instances an initial large company licensee gave the technology back to the university and it was relicensed to a spin-out which successfully developed it. For instance, the antibody that became Imclone's Erbitux was initially licensed by the University of California to Eli Lilly who subsequently terminated the license and returned it to the University of California, who relicensed it to Imclone.

When the licensee is a small company or a spin-out company, the licensor generally expects that the small company will not have the resources to take the product to market and will need to find a partner at some point along the way.

Our study in general confirmed this model. Fifty-six different companies are currently marketing the 153 products, and their distribution is radically different from that of the initial licensees who commenced development of the drugs. Marketing rights to the majority of the drugs are now held by large pharmaceutical companies, as shown in Table 6.3. Glaxo sells the most drugs that originated in public sector research, 12, reflecting their strong presence in both vaccines and HIV, followed by Johnson & Johnson (J&J) with nine and Merck, Pfizer and Bristol-Myers Squibb with eight each. However, it is noteworthy that 32 of the products are marketed by 17 biotechnology companies founded relatively recently. These companies either developed the product themselves or acquired rights to them from a third party and have thereby evolved to become fully integrated biopharmaceutical companies (FIBCOs). Indeed, a higher number of the 153 products were being marketed by biotechnology companies until the most recent round of consolidation and acquisition of biotechnology companies by major pharmaceutical companies (e.g., AstraZeneca's acquisition of MedImmune, Lilly's acquisition of Imclone, Takeda's acquisition of Millennium, and so forth).

The transactions subsequent to the initial license by which these drugs migrated to the current marketers are discussed in more detail in the section on pages 000–000.

Table 6.3 Companies currently marketing PSRI invented drugs

Current marketer	*Number*	*Current marketer*	*Number*
GlaxoSmithKline	12	Lantheus Medical Imaging	2
J&J	9	Merck Serono	2
Bristol-Myers Squibb	8	Mission Pharmacal	2
Merck	8	Otsuka Pharmaceuticals	2
Pfizer	8	AGALinde	1
Eli Lilly	6	Alexion	1
Genzyme	6	Bausch and Lomb	1
Novartis	6	Bioniche Pharma	1
AstraZeneca	5	DuraMed	1
Wyeth	5	Enzon Pharmaceuticals	1
Amgen	4	Ferring A/S	1
Bayer Healthcare	4	Fontus Pharmaceuticals	1
Eisai	4	Forest Pharmaceutical	1
Roche	3	Genentech	1
Abbott	3	Genta	1
Baxter Healthcare	3	Ipsen	1
BiogenIdec	3	J&J Merck Consumer Pharm.	1
Gilead Pharmaceuticals	3	Mallinckrodt	1
Schering-Plough	3	Mylan Bertek Pharmaceuticals	1
Allergan	2	NitroMed	1
Astellas Pharma Inc.	2	Sanofi Aventis	1
BioVitrium	2	Santarus	1
Celgene	2	Shionogi	1
Cephalon	2	Shire	1
CSL Behring	2	Specialty European Pharma	1
Galderma SA	2	Takeda	1
General Electric	2	The Medicines Company	1
King Pharmaceuticals	2	Watson Laboratories	1

Development timeline

By making certain assumptions we were able to identify the timing and duration of the various phases of the development pathway of these drugs.

INITIATION OF THE DISCOVERY PROCESS

Patents that resulted from a federal grant are required to disclose the Government's rights in the patent application. We were able to identify 84 of the discovery projects in our study as having been federally funded. Of these, 19 arose from the

NIH intramural program alone (and thus did not involve grants) and 65 acknowledged funding by federal agencies, normally from the Department of Human and Health Services (DHHS) and most frequently from the NIH, the primary research funding agency of DHHS. Four of these involved joint funding with the Veterans Administration and one each was funded by the Department of Energy and the Office of Naval Research. Three were funded by both the intramural and extramural programs.

Of the extramurally funded products, 46 provided grant numbers in the patent. One patent only noted funding by the Veterans Administration. From the Computer Retrieval of Information on Scientific Projects (CRISP)[62] database, we were able to identify the date when the grant started for 23 of the products.[63] If the patent acknowledged multiple grants, we used the earliest start date of a grant naming one of the inventors of the patent as Principle Investigator (PI). When a grant number on the face of a patent did not correspond to any grant in the database, we attempted to reconstruct an actual grant number based on inventor/PI funding information. We were unable to obtain accurate grant information for 15 patents that noted NIH or HHS grant funding, possibly reflecting errors in the reported grant numbers.

We used the start date of the grant that led to the discovery of the drug as a proxy for the initiation of the discovery process.

PRODUCT DISCOVERY

Issued patents frequently claim priority to earlier patent applications, some of which may have matured into issued patents, while others may have been abandoned in favor of the later application as part of the prosecution strategy. In some cases, this results in a protracted prosecution history. The average prosecution time was 5.0 years, with a standard deviation of ±3.5 years. The longest prosecution history we found was 19.2 years and the shortest was 0.7 years.

We used the date of the earliest patent application from which the issued patent claims priority as a proxy for the date when the invention was made. We were able to identify a date of discovery for 148 of the products. As noted above, a few of the products are based on licensed biological materials for which we could not determine an invention date using our methodology.

In Figure 6.1[64] we plot the distribution of the discovery year of the products.[65] It is apparent that the number of products discovered each year appears to have taken a significant step up, from an average of roughly one every two years through the 1960s and 1970s to six in 1980. The rate continued to climb through the 1990s.

The decline since 1992–93 should not be interpreted as indicating a decline in public sector research productivity, but rather, as we show below, reflecting the long development timelines of public sector discovered drugs. Many of the drugs discovered since this peak are still making their way through the development pipeline.

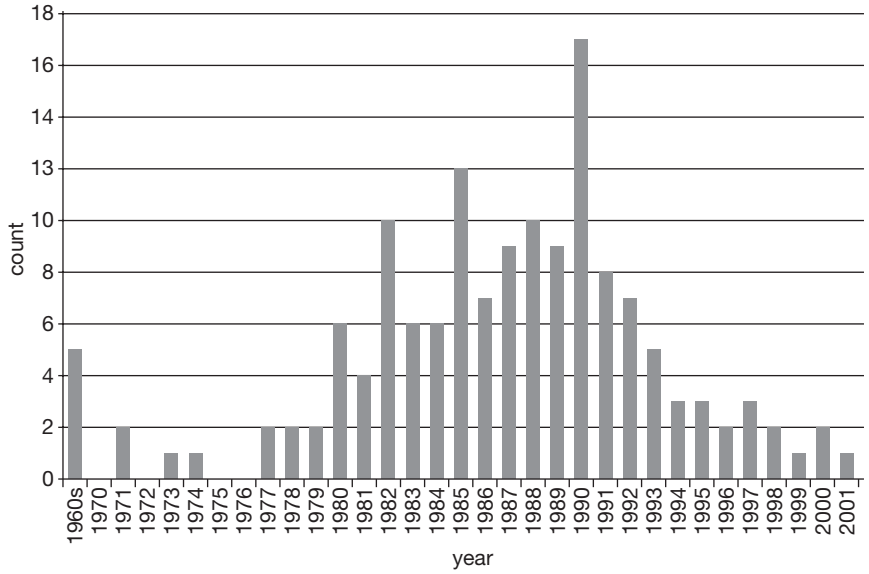

Figure 6.1 Number of PSRI discovered drugs by year

PRODUCT DEVELOPMENT

Academic institutions are rarely able to secure funding for drug development nor are they equipped with the infrastructure to take their drug discoveries very far down the development pathway. Thus, they must seek commercial licensees to develop their discoveries. We used the date of the initial license as a proxy for when preclinical and clinical development of the drug started.

When the initial licensee was a small entity the transaction was generally considered a material transaction and hence was required to be disclosed to the Securities and Exchange Commission (SEC) when the company filed to become publicly traded. In these cases we were therefore able to identify the date when the initial license was issued from Recombinant Capital's rDNA database. If the initial licensee was a large entity, the transaction was generally not considered to be a material transaction and hence was frequently not publicly disclosed or even announced. In these cases we asked the individual TTOs for the date of the transaction, and in many cases they were willing to supply this information.

If we were only able to determine the year of a transaction, we assigned it a date of July 1 of that year.

Some of the products were the result of research collaborations and we used the date of the initiation of the collaboration as the date of the license since companies are rarely if ever prepared to sponsor research at an academic institution without an agreement providing them an exclusive option to an exclusive license

to any resulting intellectual property. However, the license terms are generally negotiated at the time of exercise of the option.

We were able to determine the date of the start of development for all 153 products.

ADDITIONAL TRANSACTIONS

Using the rDNA database, we were able to identify 191 additional transactions involving the technology. As shown in Table 6.4 and presented graphically in Figure 6.2, 44 of the 153 products in our database involved only one step in the development pathway while the remaining 109 products involved at least one additional transaction. Overall, around a third of the development pathways involved only one step, a third involved two steps and the remaining third involved more than two steps.

Table 6.4 Numbers of transactions in the development pathways of PSRI invented drugs

Steps in pathway	*Number of products*
1	44
2	53
3	37
4	14
5	3
6	2
	153

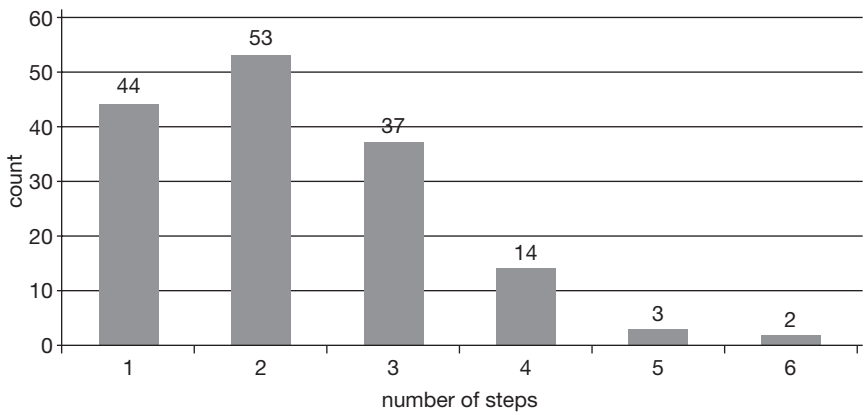

Figure 6.2 Numbers of transactions in the development pathways of PSRI invented drugs

We classified these additional transactions as to whether they occurred before or after FDA approval of the drug. The results are shown in Table 6.5. There are more additional transactions *after* FDA approval than before FDA approval.

Table 6.5 Number and timing of additional steps in the development pathways of PSRI invented drug pre- and post-FDA approval

Initial license	153	
Transactions pre-FDA approval	88	
Of which:		
Transaction 2		68
Transaction 3		14
Transaction 4		5
Transaction 5		1
Transactions post-FDA approval	103	
Of which:		
Transaction 1		75
Transaction 2		25
Transaction 3		3

PRODUCT APPROVAL

The date of product approval was obtained from the FDA CDER and CBER websites. We were able to identify the date of FDA approval for all 153 products in our database. Some drugs received multiple approvals (e.g., for additional indications, formulations or combinations). Two NMEs each received five NDAs.

We identified all the NDAs and BLAs approved for the molecular entities in our study. If a combination therapy contained two compounds which were both discovered in public sector institutions (e.g., Glaxo's Epzicom, a combination of Epivir, discovered by Emory University and Ziagen, discovered by the University of Minnesota) we only counted the NDA once.

Of the 108 compounds approved under NDAs in this time period, 32 had more than one NDA approved.

These 108 compounds had a total of 158 NDAs approved. The highest number of NDAs for a single active compound was five, for voriconazole, the active ingredient in Pfizer's Vfend.

Only one molecular entity had more than one approved BLA – filgrastatim, the active ingredient in Neupogen, where a PEGylated version with a substantially longer serum half life was approved as Neulasta.

The distribution of the number of NDAs and BLAs per molecular entity is shown in Figure 6.3. In Figure 6.4, we plot the number of drugs receiving their first NDA or BLA each year. In Figure 6.5 we plot the date of approvals of all NDAs and BLAs each year.

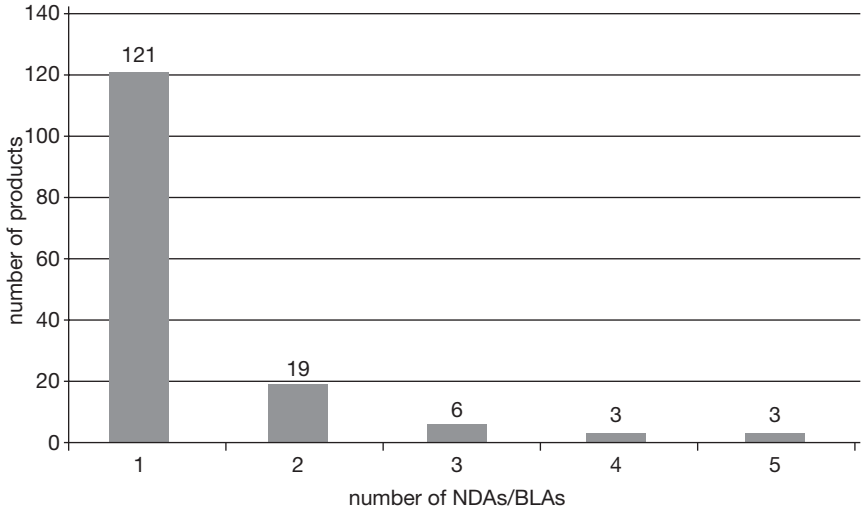

Figure 6.3 Number of BLAs/NDAs received per product for PSRI invented drugs

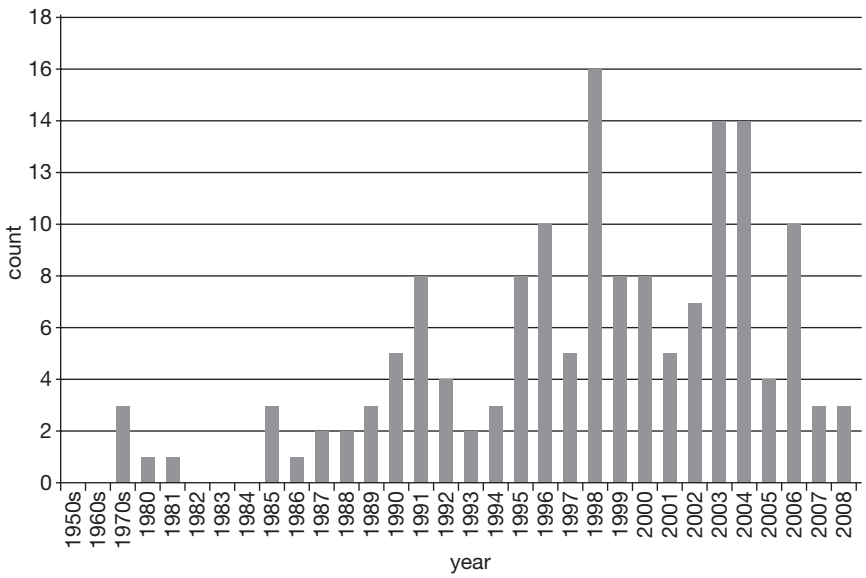

Figure 6.4 Year of approval of initial BLA/NDA for PSRI invented drugs

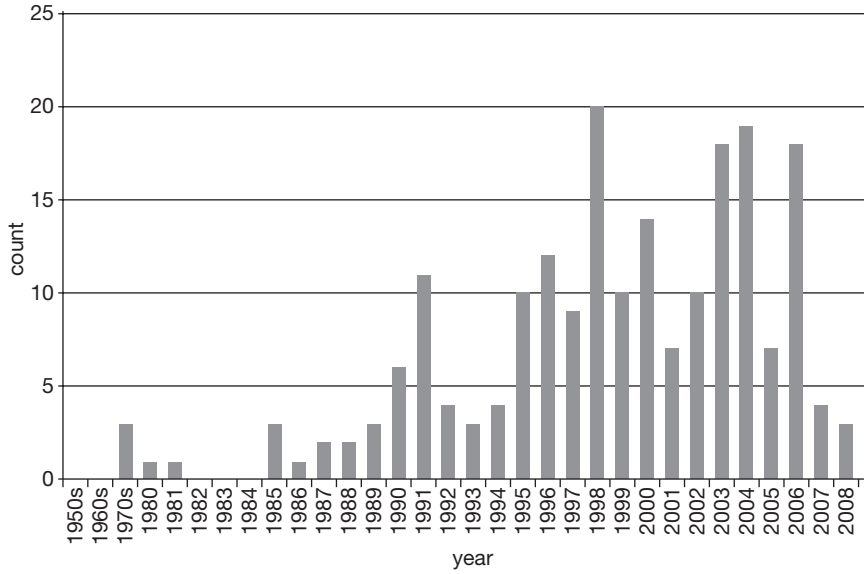

Figure 6.5 Year of approval of all BLAs/NDAs for PSRI invented drugs

RESULTS

The results of our investigations into the duration of the different phases are shown in Table 6.6 below.

The timelines are highly variable in length and reflect the highly diverse nature of the relationships we identified:

- Collaborative research projects that resulted in discovery of the product;
- Independent academic research that resulted in the discovery which was subsequently licensed to the corporate partner;
- Arrangements to avoid or preempt negative consequences of interference proceedings; and
- Situations where litigation resulted in an infringement judgment against the developing company and hence acceptance by the developing company of the validity of the PSRI's patent.

Table 6.6 Overall timelines of phases of product discovery and development of PSRI invented drugs

Phase	*N*	*Mean*	*Median*	*Maximum*	*Minimum*	*Std. Dev*
Start of research to discovery	22	5.57	4.22	16.70	0.75	3.75
Discovery to initial license	148	3.27	2.13	24.12	(9.09)	4.91
Initial license to FDA approval	153	8.10	8.24	23.00	(13.22)	5.39
Discovery to FDA approval	148	11.46	10.98	26.99	1.27	4.94

In the first of these situations, the date of the license will precede the date of discovery, while in the last, the date of the license will generally be subsequent to the date of FDA approval.

We show the distribution of the time from discovery through to FDA approval in Figure 6.6. The average time from discovery of the drug to FDA approval was 11.5±4.9 years of which the average time between the discovery and the initial license that initiated the development process was 3.3±4.9 years, while after the license was in place, the average time to FDA approval was 8.1±5.4 years. Based on a somewhat smaller number of data points, the discovery phase lasted an average of 5.6±3.8 years.

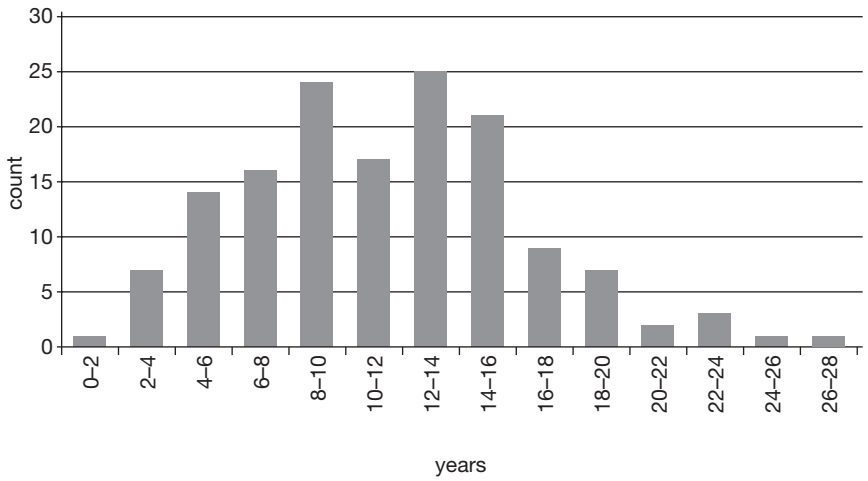

Figure 6.6 Distribution of timelines from invention to initial FDA approval for PSRI invented drugs

Development pathway

There have generally been thought to be two pathways for commercializing academic technologies:

- A one step pathway when the initial licensee is a large company which develops the technology and takes it to market itself:

  Academic Institution ➔ Large Co ➔ Market

- A two step process when the initial licensee is a spin-out or other small company, which carries out the early stage, high risk research to prove the viability of the technology and which subsequently partners with a large company for access to funding for the late stage, higher cost phases of development, manufacturing, global distribution and so forth, i.e.:

Academic Institution ➔ Small Co ➔ Large Co ➔ Market

However, one of the most surprising findings of our study was that both of these pathways are vast over-simplifications and Table 6.7 shows how the number of steps in the development pathway varies between the three categories of initial licensee.

As would be expected, where the initial licensee is a large company, a majority of the companies take the product to market themselves and there are no further transactions. However, in almost 40% of the cases, there are additional transactions. The additional transactions included:

- Termination of the initial large company partnership and replacement with a new partnership;
- Co-promotion agreements;
- Assignment of the license;
- Acquisition of the developing company;
- Acquisition of the product; and
- Monetizations of royalty streams.

In the cases where the initial licensee is a small company, the situation is reversed, with additional transactions in 94% of the cases. While 48% of the cases were the "classical" two step pathway, 44% had more than two steps. Notably, however, for five products (6% of the total), there were no further transactions and the small company is currently marketing the product itself. Our data clearly show therefore that the two step development pathway is a considerable over-simplification, with a consistent pattern of additional transactions, both before and after FDA approval of the product.

Products where the initial licensee was a spin-out company are skewed even more heavily towards a larger number of steps in the development pathway. In only one, or 3.5%, of the cases is the spin-out company marketing the product themselves while 35% of the cases involve a two step pathway and 60.5% of the cases involve three or more steps.

Table 6.7 Numbers of steps in development pathway of PSRI invented drugs by different types of initial licensee

Initial licensee	*Number of steps*						
	1	*2*	*3*	*4*	*5*	*6*	*Total*
Large entity	39	14	10	1	1	0	65
Small entity	4	31	18	10	1	1	65
Start-up	1	8	9	3	1	1	23
	44	53	37	14	3	2	153

One of the most complex pathways we identified is that for Macugen, a drug for the treatment of acute macular degeneration, which was discovered at the University of Colorado and involved seven transaction steps. The complete timeline of Macugen's development is as follows:

- The initial patent was filed by the University of Colorado in June 1990;
- The patent application was licensed by the University of Colorado to NeXstar in June 1991 for $1 million in stock and sponsored research funding;
- NeXstar was acquired by Gilead in 1999 for $550 million in stock;
- Gilead sublicensed rights to NX1838 to Eyetech, a new company, in 2000 for $7 million upfront and $25 million in milestone payments;
- Eyetech and Pfizer entered a Co-promotion agreement in 2002 for $75 million upfront, $25 million in equity purchase, $195 million in approval milestones and $450 million in post-approval milestones;
- The FDA approved Macugen in December 2004;
- The University of Colorado monetized part of its royalty interest in Macugen in January 2005 for an estimated $45 million;
- Eyetech was acquired by OSI Pharmaceuticals in June 2005 for $935 million in stock and cash;
- In August 2008, OSI divested its eye care business, primarily Macugen, to a new company, Eyetech, which primarily consisted of the Macugen salesforce, in exchange for potential future milestone and royalty payments.

There were six steps in the commercialization pathway of Rotarix, including three royalty monetizations, two by Children's Medical Center, Cincinnati, and one by Avant Therapeutics, the company formed by the merger of the initial licensee, Virus Research Institute, with T Cell Sciences.

Economic impact

Public sector discovered drugs have an economic impact at several levels:

- On the discovering institutions;
- On the developing companies; and
- On the marketing companies.

Economic impact on the discovering institutions

When a university licenses a drug to a company, the terms normally include a series of payments to the university. There will generally be an upfront fee, annual minimum royalty payments, milestone payments as the drug reaches key stages in its development and finally royalties on sales.

A recent study[66] collected and analyzed data on 155 transactions completed between 2005 and 2007 on drugs at all stages of development when the licenses

were completed. 35% of the deals were from academic institutions. The study analyzed the deals by stage of development:

1 Preclinical;
2 IND filed through Phase II enrolled;
3 Phase II completed through Phase III enrolled;
4 Phase III completed through NDA submitted;
5 Marketed.

The study did not analyze the deals by type of licensor. Public sector discovered drugs will fall in group 1, but this group will also include deals by biotechnology companies who have advanced the drug further in development than a university typically will have been able to do, which will probably allow them to command a higher royalty rate.

For this group, the study found that, for deals with fixed royalty rates, the royalty rate averaged 4.2%, while those with tiered royalty rates had royalty rates that averaged from 4.5% on sales of less than $50 million to 7.5% on sales of $1 billion and more.

A 5% royalty on a drug with sales of $100 million would yield annual royalties of $5 million to the licensor, while a 7.5% royalty on sales of $1 billion would yield annual royalty payments of $75 million to the licensor.

The AUTM Annual Licensing Activity Survey (ALAS) shows that total royalty receipts by academic institutions have grown strongly since 1991, from $170 million to $3.4 billion in 2008. Royalties from marketed drugs have been substantial contributors to this increase in royalty income.

Most institutions have multiple licenses generating royalty income, so it is, in general, not possible to identify the income generated by each drug. However, over the past decade or so, institutions receiving royalties on drugs that have received FDA approval have started monetizing those royalty streams by selling the royalty obligations, sometimes back to the licensee or, more commonly, to partnerships which specialize in acquiring royalty streams and it is possible to identify the value of these monetizations. Table 6.8 identifies 35 royalty sales by academic institutions with a total value of $4.1 billion completed since 1990, with the pace appearing to have increased since 1999. We have included all monetizations that we have identified of drugs approved prior to our data collection cut-off of August 31, 2009, even if the monetization occurred subsequent to this date.[67]

Economic impact on the developing company

The multi-step development pathways identified in in the section on pages 000–000 were the result of a large number of transactions. We were able to track the reported value of many of these transactions in ReCap.[68] A certain amount of judgment was necessary in this exercise. For instance, in April 2007, AstraZeneca acquired MedImmune for $15.7 billion. The majority of MedImmune's drugs

Table 6.8 Sales of royalty streams from PSRI invented drugs by academic institutions and/or the inventors

Date	*Product*	*Licensor*	*Amount ($mm)*	
6/1/90	Neupogen	Amgen	$75	
1/1/97	Synagis	Henry M. Jackson Foundation, Inventors	n/a	
1/1/98	TOBI	Seattle Children's Hospital	$12	
1/1/98	Thalomid	Children's Hospital	$5	
1/1/98	Taxol	Robert Holton (Florida State U.)	$32	*
1/1/98	Remicade	Jan Vilcek (NYU)	$66	
1/1/98	Enbrel (Foreign)	Hospital, Inventors	n/a	
12/1/99	Zerit	Yale University[1]	$125	
1/1/01	Clarinex	Inventor	n/a	
1/1/03	FluMist	University of Michigan	$10	**
1/1/03	AdVate	University of Connecticut	n/a	
9/1/03	Aldurazyme	LA Biomed[2]	$25	
1/22/04	Neupogen/Neulasta (US)	Memorial-Sloan Kettering[3]	$263	
1/1/05	Macugen	University of Colorado[4]	$45	
6/28/05	Tysabri	Fred Hutchinson Institute	n/a	
7/1/05	Emtriva	Emory University[7]	$525	
8/1/05	Remicade	NYU/Dr. Vilcek	$46	**
8/1/05	Neupogen/neulasta (Non-US)	Memorial-Sloan Kettering[8]	$142	
10/26/05	Humira	Scripps Research Institute[9]	$34	*
11/1/05	Rotarix	Children's Hospital Cincinnati Inventors	n/a	**
12/14/05	Rotateq	Wistar Institute[6]	$45	*
6/6/06	Embrel (US)	MGH[10]	$248	
4/1/07	Revlimid	Children's Hospital Boston	$131	
4/19/07	Enbrel (Foreign)	MGH[11]	$284	
5/1/07	Remicade	New York University[12]	$650	
7/1/07	FluMist	U. of Michigan[13]	$25	
12/1/07	Rotarix	Cincinnati Children's Hosp.[15]	$24	
12/18/07	Lyrica	Northwestern[14]	$700	
1/1/08	Relistor	U of Chicago Inventors	$8	
4/23/08	RotaTeq	Children's Hosp. of Phil.[16]	$182	
9/1/09	Myozyme/Lumizyme	YT Chen (Duke inventors)	$30	
2/1/11	Somavert	Ohio University	$52	
1/1/12	Myozyme/Lumizyme	Duke	$90	
3/12/12	Botox	U. of Colorado [18]	$30	
1/5/13	Lyrica	Northwestern Inventor	$148	**
	Total		$4,051	

* Estimate
** Sale by inventor

were discovered at PSRIs, so we attributed this transaction to the PSRI drugs and included the transaction in our analysis. By contrast, in March 2001, Johnson & Johnson acquired ALZA Corporation for $10.5 billion. Very little of ALZA's sales were from PSRI discovered drugs, so this transaction is not included in our study. We also did not include in the calculations the various major pharmaceutical company-pharmaceutical company mergers over the past decade – e.g., Pfizer's mergers with Pharmacia & Upjohn, Warner-Lambert, Wyeth-Ayerst, etc., though many of these companies were selling one or more PSRI discovered drugs.

We were able to identify the valuation of 23 of the 153 initial licenses and 144 of the 191 additional transactions. Over $143 billion was realized in the 144 transactions which followed the initial license transaction as shown in Table 6.9.

The average value per transaction is presented graphically in Figure 6.7.

In instances where there are a substantial number of transactions to provide meaningful data, the data show a steady increase in the value of technologies as they move from the initial license from academia into development and receive FDA approval.

The highest step up in valuation is with the first transaction after the initial academic license, where the mean value was 44 times higher than the initial academic license. Relatively few academic license valuations are in the database and they all have low valuations, reflecting the early stage nature of most academic technologies. It is extremely difficult to obtain federal funding for lead optimization, pre-clinical studies and toxicology, let alone clinical testing, so academic licenses are typically done at a very early stage. By contrast, the initial developer will generally develop the technologies to a significant value-added milestone before seeking a large company partner, so subsequent transactions are concluded at much higher valuations.

After the second transaction, valuations increase approximately two and a half-fold between each transaction for technologies with a substantial number of

Table 6.9 Number and value of transactions in development pathways of PSRI invented drugs

Transaction	*Number*	*Value**	*Avg. value / transaction**
Initial License	23	$99.0	$4
Transaction 2 Pre-FDA App.	51	$9,634.7	$189
Transaction 3 Pre-FDA App.	11	$5,522.0	$502
Transaction 4 Pre-FDA App.	5	$1,194.0	$239
Transaction 5 Pre-FDA App.	1	$24.0	$24
Transaction 1 Post FDA App.	54	$70,308.4	$1,302
Transaction 2 Post FDA App.	20	$56,002.2	$2,800
Transaction 3 Post FDA App.	2	$443.0	$222
Total	167	$143,227.3	

* Dollars are in millions

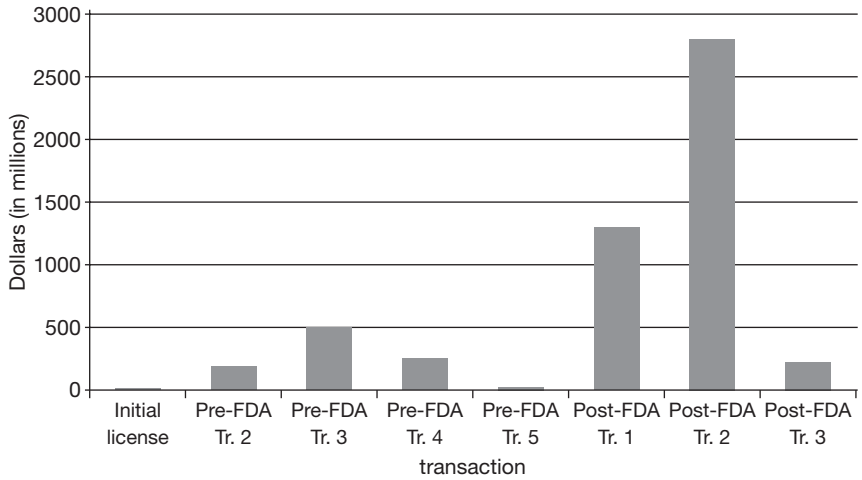

Figure 6.7 Average value of each transaction in development pathways of PSRI invented drugs

transactions – the third transaction pre-FDA approval and the first and second transaction post-FDA approval. There are relatively few technologies which had four or five transactions before FDA approval or three transactions after FDA approval, and in these cases, valuations stepped down. These transactions may be indicative of the technology being "distressed".

Probably the greatest economic impact of the commercialization of public sector research is the market value of the successful companies that have resulted from having commercialized a public sector discovered drug. For instance, Amgen currently has a market capitalization of around $50 billion. Amgen is currently selling 4 drugs that resulted from public sector research (Enbrel, Neulasta, Neupogen and Sensipar), recently sold two others (Kepivance and Kineret) to BioVitrum in a $130 million transaction and, as noted above, sells two other major drugs, Epogen and Aranesp, which resulted from research carried out but not patented at the University of Chicago. Virtually all of Amgen's market capitalization can therefore be attributed to the results of public sector research. However, creation of this market capitalization required an enormous private sector investment to achieve. Analysis of the private sector investment needed to translate these public sector investments into marketed products is beyond the scope of this study.

Economic impact on the marketing company

The 2008 sales data for these drugs was kindly provided by IMS Health. The search was carried out by generic name and then by brand name. Branded generic sales were normally reported individually and all other generics as a single figure.

For Topamax, Gleevec and Botox, where only selected indications were invented in the course of public sector research, the sales for the relevant indications were obtained from IMS Health, Inc.'s National Sales Perspectives™ and National Disease Therapeutic Index™. For all other products, the data was obtained from IMS Health, Inc.'s National Sales Perspectives™.

Patent expiration had occurred for a number of the products and generic versions were available. Sales of generics were examined on a case-by-case basis to determine whether the generic formulations targeted the same indications as the brand version that originated in public sector research. For instance, Sarafem is a brand of fluoxetine hydrochloride approved for treatment of premenstrual dysphoric disorder (PMDD), a use discovered and patented by MIT. However, fluoxetine hydrochloride is better known as Prozac and we assumed that the majority of sales of generic fluoxetine hydrochloride are for treatment of depression, not PMDD, so only sales of Sarafem itself and of a branded generic called Selfemra specifically targeted to the PMDD market are included in the total.

The distribution outlets covered include Retail (Chains/Mass Merchandisers, Food Stores, Independents) Clinics, Mail Service, Non-Federal Hospitals, Long Term Care, Home Health Care, Federal Facilities, HMO, Misc-Prisons, Misc-Other, and Misc Universities but does not include sales from Long Term Facilities.

Eight products in this study were only identified after the data request was submitted to IMS Health. We were able to determine 2008 sales of all but one of these from company reports and we added these to the IMS data.

Certain drugs are sold to physicians who administer them in their office and are not captured by IMS's methodology. This is particularly true of Genzyme's enzyme replacement products Aldozyme and Myozyme. The sales reported in Genzyme's annual report were significantly higher than those reported by IMS and we included these figures in our analysis.

Total US sales of PSRI discovered drugs in 2008 were $39.9 billion. IMS reports on its website[69] that total US pharmaceutical sales were $291.5 billion in 2008, so PSRI discovered drugs accounted for 13.7% of the total.

IMS also reports that the global pharmaceutical market was $773.0 billion in 2008, so that the US market accounts for 37.7% of the global market. Assuming that US sales of PSRI discovered drugs are also 37.7% of the drugs' global sales, we estimate worldwide sales of the public sector discovered drugs to be $102.7 billion.

Twenty-one of the products had no sales in 2008 or had been withdrawn from the market.

The FDA conferred orphan drug status on 36 of the 102 NME products in our study, meaning that they treated a patient population of fewer than 200,000 patients. Three of the biologics also received orphan designation.

Twenty-eight of the products achieved blockbuster status with sales of over $1 billion worldwide while 12 of these had sales of over $1 billion in just the US. The three top selling drugs – Enbrel, Neulasta and Remicade – each had estimated worldwide sales of around $8 billion.

Comparison with other countries

We have initiated a comparable study of the contribution of PSRIs outside the US to the discovery of marketed drugs. We have so far identified 38 drugs discovered in nine countries. The drugs are shown in Table 6.10.

Table 6.10 Drugs discovered by non-US PSRIs

Drug	*Discovering institution(s)*	*Country*
Drugs not included in current study		
Ambisome	U. of British Columbia	Canada
Atracurium	U. of Strathclyde	UK
BioHep	Weizmann Institute of Science	Israel
Campath	Cambridge U.	UK
Copaxone	Weizmann Institute of Science	Israel
Daunoxome	U. of British Columbia	Canada
Exelon	Hebrew University of Jerusalem	Israel
Ferriprox	U. of Essex	UK
Frone	Weizmann Institute of Science	Israel
Hepsera	Academy of Sciences/ Katholic University in Leuven,	Czech Republic, Belgium
Interferon	MRC	UK
Ixempra	Helmholtz Centre for Infection Research	Germany
Levulan	Queen's University	Canada
Myocet	U. of British Columbia	Canada
Navelbine	CNRS	France
Periochip	Hebrew University of Jerusalem	Israel
Rebif	Weizmann Institute of Science	Israel
Relenza	CSIRO, Monash University	Australia
Removab	Helmholtz Zentrum München	Germany
Selectiose	CNRS	France
Taxotere	CNRS	France
Telbivudine	CNRS	France
Temodar/Temodal	Imperial College London/Aston University	UK
Tiorfan	Inserm	France
Tomudex	Institute of Cancer Research	UK
Varivax	Biken Institute at Osaka University	Japan
Viread	Academy of Sciences/ Katholic University in Leuven,	Czech Republic, Belgium
Vistide	Academy of Sciences/ Katholic University in Leuven,	Czech Republic, Belgium

Drug	*Discovering institution(s)*	*Country*
Drugs included in current study		
BeneFIX	University of Oxford	UK
Doxil	Hebrew University of Jerusalem	Israel
Epivir-HBV	University of Alberta	Canada
Erbitux	Yeda Research & Devel.	Israel
Gardasil	German Cancer Research Centre/ U. of Brisbane	Germany, Australia
Hepatitis B	Edinburgh	UK
Humira	MRC	UK
Sutent	Max Planck Society	Germany
Visudyne	University of British Columbia	Canada
Zinecard	CRC	UK

Of these drugs, 28 are not included in our US study, indicating that the discovery was made entirely by non-US institutions, while ten are also included in the current study, implying that both US and non-US public sector researchers made a contribution to the discovery of the drug. The discovering countries are shown in Table 6.11.

It is noticeable that these countries have contributed significantly fewer new drugs than their U.S. counterparts despite a comparable overall level of combined total spending on scientific research in these countries. One possible explanation for this difference is that for the majority of the study period, professors owned the rights to their inventions throughout most of Europe – the so called "Professors' Privilege" or "Teachers' Exemption". Only towards the end of the 1990s did most European countries adopt the US model, and today only in Sweden do the rights to academic inventions still reside with the professor. European institutions are now establishing offices of technology transfer at a rapid rate, though funding for these activities is an issue.

Table 6.11 Countries of domicile of non-US PSRIs that invented FDA approved drugs

Country	*Number*
UK	10
Israel	8
Canada	6
France	5
Germany	3
Belgium	3
Czech Republic	3
Australia	2
Japan	1

It is noteworthy that the UK, where a similar, institutional model of ownership to that established by the Bayh-Dole Act was introduced in 1988,[70] has the next most productive PSRIs. However, the number of drugs is substantially ~~less~~ than those discovered by US institutions. One of the reasons may be lower levels of funding for scientific research. In addition, substantial funding for technology transfer activities at the individual institutional level did not become available in the UK until around 1999, when "third stream" funding schemes were introduced. A recent article discussed in some length the much lower inclination of public sector research researchers in Europe to patent the results of their research.[71]

Discussion

There is little dispute that the pharmaceutical industry relies heavily on the results of basic scientific research carried out in the public sector to identify promising points of intervention at which to target drug discovery efforts.

However, there have been far fewer studies of the actual role of public sector research in the discovery of new drugs.

Our results are consistent with those of Kneller,[72] who looked at the discoverers of NME and new biologics approved between 1998 and 2007, updating an earlier study that had just looked at approvals from 1998 to 2003.[73] For this limited subset, Kneller found that 44.1% of all 252 NMEs and new biologics approved by the FDA during this time period originated from outside the large pharmaceutical companies; 2.5% originated in small pharmaceutical companies, 17.5% originated with biotech companies and 24.1% originated from PSRIs. Of the drugs that originated from public research, 35.2% were licensed to pharmaceutical companies and the balance was licensed to biotech companies. The PSRI contribution was 27.7% of NMEs given priority review, 17.6% of NMEs given standard review and 35.3% of new biologics.

Conclusions

We believe that two factors contributed to the increase in PSRI research productivity in drug discovery that started in 1980. On a technical level, the 1980s saw the automation and widespread diffusion of the fundamental techniques of biotechnology – recombinant DNA and monoclonal antibodies – beyond the academic institutions in the UK and on the east and west coasts of the US that had discovered them in the mid-1970s. While these techniques were available to the traditional pharmaceutical companies, they were clearly disruptive technologies and enabled the creation of numerous new drug discovery companies normally founded by the discovering professors and funded by venture capitalists. These companies licensed the drug discoveries those professors had made and started developing them.

However, one must look further to explain the increase in the public sector role in the drug discovery process. As we discussed above, in 1980 the Bayh-Dole Act allowed and incentivized academic institutions to protect and license their intellectual property, while the Stevenson-Wydler Act, along with the 1986

amendments under the Federal Technology Transfer Act provided similar incentives to federal laboratories. Our data appears to provide strong, albeit circumstantial, evidence that these Acts achieved their public policy objectives of facilitating the movement of publicly funded technologies to the marketplace for the benefit of the public.

We believe this study provides some of the most compelling data yet generated that these policy changes regarding the ownership and exploitation of the results of public sector research have had their desired effect, regardless of the source of funding. Our study shows that PSRIs:

- Increased the rate at which they identified and patented healthcare innovations as soon as the Acts were passed;
- Successfully licensed those innovations to companies that brought them to market;
- Displayed a preference for small businesses in their licensing, with 57.5% of the initial licensees being small entities;
- Discovered drugs that had a high medical impact, accounting for 21.1% of New Molecular Entities given priority review by the FDA over an 18-year period;
- Discovered drugs whose estimated worldwide sales in 2008 were over $100 billion, including twenty eight "blockbusters" with sales over $1 billion; and
- Contributed significantly to the treatment of rare diseases, with 36% of the NDAs approved receiving Orphan Drug designation.

Our study also showed that commercializing the results of private sector research:

- Created substantial wealth in the private sector, with $143 billion of capital value realized in transactions;
- Resulted in the creation of a number of sustainable, profitable fully integrated biopharmaceutical companies with substantial market capitalizations; and
- Resulted in substantial royalty streams to some of the institutions that have discovered these drugs, some of which have been monetized, resulting in substantial one time payments.

In short, one of the objectives of the Bayh-Dole Act was to integrate academic research into the commercial mainstream and our study shows that in the drug sector, at least, this objective seems to have been achieved.

Whenever the topic of drugs that were discovered in the public sector with public funding comes up in discussion, the next question is inevitably "Well, if the Government paid for this drug's discovery, why does it cost so much?" The large number of drugs we have identified in this study to have resulted from publicly funded research may elevate this discussion to a new level.

However, it is important to note that public sector research only pays for the *discovery* of these drugs. The cost to develop a drug is greater by at least two orders of magnitude and must be funded by the private sector. The only drug we have identified where substantial public funding was used in its development was

Taxol, where no patent protection on the composition of matter or use was available. The NCI invested $484 million to discover and develop Taxol from 1977 through 2002.[74] Bristol-Myers Squibb, who obtained exclusive rights to the Government's data through a Cooperative Research and Development Agreement (CRADA) with NCI which commenced in 1991, reported to the General Accounting Office that it spent an additional $1 billion on the development effort.

Our study was unable to discover either the expenditures by the public sector researchers to discover these drugs or the expenditures by the private sector to develop them.

- When we did the study, the dollar amount of grants was confidential and was not accessible via CRISP, so we cannot estimate the cost to discover these drugs. Anecdotally though, federal grants are typically in the $150,000–$500,000 per year range. Our data showed a time of 5–6 years from the start of a grant and the discovery of the drug, indicating that discovery costs are likely to be in the $1–5 million range. Subsequently, the amount of funding is available from the REPORTer system back to 1990.
- The pharmaceutical industry resolutely refuses to disclose the cost of developing individual drugs. There are the much-quoted figures of $800 million to $1.2 billion as the cost to develop a drug from the Tufts Center for the Study of Drug Development. However, these are the total economic cost of discovery and development and not the cost of developing an individual drug. The largest cost is the cost of failure while the second highest cost is the opportunity cost of capital. The out of pocket cost to conduct the pre-clinical and clinical development cost of an individual drug is a distant third, and is typically $200–500 million per drug.

Occasionally, it is possible to get hard data. Abbott laboratories received a $3.5 million grant from the NIH and used it to successfully discover Norvir, the first HIV protease inhibitor. In December 2003, Abbott raised the price of Norvir five-fold. This precipitated an outcry from the AIDS community and a march-in petition under Bayh-Dole was made. During an NIH committee hearing on the subject, Jeffrey M. Leiden, president of Abbott's pharmaceutical products group, said that the clinical development of Norvir had cost Abbott over $300 million.[75] The development cost was therefore 85 times higher than the discovery cost.

There is therefore a roughly 100- to 200-fold greater private sector investment needed to translate the public sector's investment in discovery into a marketed product. The imposition of price controls as a condition for rights to license a publicly discovered drug would certainly stop companies from making these substantial investments, thereby throwing out the baby with the bath water.[76]

The final issue that our study may raise is whether the Government should share in the substantial royalty income that some public sector institutions have received from successful federally funded drug discoveries. Such a provision was included in the initial draft of the Bayh-Dole Act but was taken out in the discussion on the Senate floor because it was decided that the Government's

financial return should come from the taxation on the increased economic activity that would result from the commercialization of federally funded inventions. Studies have shown that the Government has received a far greater financial return through taxation by stimulating this economic activity then it would have received by collecting a fraction of the discovering institution's royalty income.[77]

Overall the public and private sector research programs in the US complement each other very effectively. While the traditional model which strictly divided basic and developmental biomedical research between the two sectors no longer applies, each sector plays an important role. The private sector is needed to conduct most of the developmental research as well as to manufacture and sell drugs. On the discovery side, the private sector discovers most of the new drugs, including many highly innovative ones. However, we have shown that between 10 and 20% of new drugs are discovered in the public sector, sometimes in collaboration with the private sector. Most interestingly, the public sector contribution is proportionally more than twice as innovative as the private sector.

Public sector researchers pursue new scientific fields of inquiry and are able to take more scientific risks than private sector researchers. They are also not limited in their research by business constraints to seek drugs for the most profitable markets. This may explain why the public sector has the greatest contribution to new vaccines, which have some of the lowest profit margins among biomedical products and a higher risk associated with safety because healthy people are vaccinated. Hopefully, this study will lead others to explore further how and why public sector researchers are more innovative.

This study raises tantalizing questions about how the retrenchment of the pharmaceutical industry from translational research might affect the contribution from publicly funded research to the discovery of new drugs and vaccines. The pharmaceutical industry's current narrow focus on target-based drug discovery leaves all sorts of cutting-edge knowledge, such as stem cells or nanotechnology, sitting "on the shelf", waiting to be translated into something useful. Traditionally, universities and public research institutions have stepped in and filled the void, but such cutting edge technologies are normally initially developed by venture capital backed companies, who make the necessary investment to prove the technology viable. Many technologies take 20 to 25 years from initial discovery to the regulatory approval of its first product. This is a long time period for venture capital and if the technology is sufficiently fraught with difficulty – such as gene therapy – venture capital eventually looses patience, investment reverts to what can be raised from basic science funding sources and progress slows to a crawl. The long history of gene therapy bears this out. The problem for the future is that venture capital is itself retrenching after 15 years of poor returns. Currently, the mantra among venture capitalists is that they are happy to start a company when the technology is a year away from entering Phase 1 testing. The challenge for academic institutions is to find the funding to bridge technologies through this "valley of death". Initiatives such as the NIH's Research Evaluation and Commercialization Hub (REACH) Awards, the NCI's Experimental Therapeutics Program (NExT) and NHLBI's Centers for Accelerated Innovations (CAI) could be crucial in this regard.

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Notes

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38 Glaxo Annual Report 2004.
39 www.investor.bayer.com/user_upload/34/
40 http://jolt.law.harvard.edu/digest/patent/ex-parte-pfizer-inc
41 John Maroney, Personal communication.
42 www.autm.net/about/dsp.licensing_surveys.cfm
43 It is permissible to withhold a US patent application from publication if, at the time of filing, the applicant has decided not to file international applications claiming priority to the US application. This is unlikely to be the case for patent applications for pharmaceutical products because of the need to recover development costs from a worldwide market.
44 www.rdna.com/
45 Public Benefits Survey, Association of University Technology Managers, Deerfield IL, 1994. The 1996 study was not published, for reasons that are not clear, but AUTM made it available to us.
46 www.betterworldproject.net/products/index.cfm (accessed August 3, 2008).
47 www.uvapf.org/index.cfm/fuseaction/viewpage/page_id/115?CFID=1450853&CFTOKEN=54000268& (accessed August 3, 2008).
48 www.ott.nih.gov/about_nih/fda_approved_products.html (accessed August 3, 2008).
49 http://s-edison.info.nih.gov/iEdison/commercial_report.jsp. The requirement for grantees to report FDA approved products that include technologies invented with NIH funded began for FDA approvals after January 2003.
50 www.dricapital.com/; www.paulcap.com/InvestmentPlatforms/Healthcare/PortfolioInvestmentsList.aspx; www.royaltypharma.com/casestudies/cs-main.html
51 Anand, Geeta (2006). "Mothers' Tale, As Their Babies Tested New Drug, A Friendship Grew." Geeta *WSJ* December 12: p A1.
52 Harvard Business School Case 9-502-006, Professor John T. Gourville.
53 http://patft.uspto.gov/
54 www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name
55 www.accessdata.fda.gov/scripts/oc/ohrms/frsearch.cfm
56 "Ensuring Policy and Laws Are Both Effective and Just: Academic Patents and Access to Medicines in Developing Countries," *American Journal of Public Health* 99: January 2009.
57 Based on the statement of government interests in issued patents. Note that NIH intramural inventions do not identify a grant number because intramural investigators do not receive grants.
58 After data collection and analysis was completed, the FDA approved Allos Therapeutics' NDA for Folotyn (pralatrexate) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma on September 24, 2009. Pralatrexate was first synthesized by SRI International as a potential improved analog of edatrexate, an earlier anti-folate developed by SRI International and MSKCC. Preclinical development was performed by MSKCC and Southern Research Institute. SRI, MSKCC and Southern Research Institute licensed the technology to Allos in January 2003 when the drug was in Phase II trials (www.southernresearch.org/press/pr20090925.html).
59 We excluded drugs such as thyroxine, coumadin, nystatin, penicillin, streptomycin, neomycin, 5-fluorouracil, and the contraceptive pill that were discovered in the course of public sector research and introduced before the Kefauver Harris Amendment (Drug Efficacy Amendment) of 1962 ushered in the modern era of FDA regulation of drug approvals.
60 The other driver of Amgen's growth was Epogen, which was based on research carried out by Eugene Goldwasser at the University of Chicago, but not patented nor therefore licensed by the university. In accordance with our criteria, therefore, Epogen is not included in our study. The story of Amgen and Epogen is discussed in some detail in

Merrill Goozner's 2004 book *The $800 Million Pill: The Truth behind the Cost of New Drugs*. Berkeley and Los Angeles, CA: University of California Press.

61 The Bayh-Dole Act and the Stevenson-Wydler Act require recipients of federal funding to give small businesses in the US preference in granting licensees to their inventions. 35 USC §202(c)(7)(D) and 35 USC §209(c).

62 http://crisp.cit.nih.gov

63 Since a grant retains the same number through any number of competitive renewals, sometimes lasting decades, the grant start date is the original starting date of the grant. Since it is not possible from this database to identify the competitive cycle in which the invention was made, this number, the time in years for grant "start of research to discovery" in Table 6.6, will by definition be longer for inventions made in later years of a entire grant period.

64 This figure initially appeared in the NEJM article.

65 Note that the first column is for all drugs discovered prior to 1970.

66 BioPharmaceutical Royalty Rates and Deal Terms Report (2008). In J. Schaible, and J. McCarthy (eds), Licensing Executives Society (USA and Canada), Inc.

67 One monetization (Duke's January 2012 monetization for $90 million) was Duke's royalty streams from both Myozyme and Lumizyme. Lumizyme was approved on May 24, 2010, and so is outside the data cut-off window. It was not possible to determine how much of the monetization was for Lumizyme.

68 We follow the convention of the biotechnology industry and use as the "value" of a transaction the total of all the upfront and other pre-commercialization payments. This figure does not include future royalty payments because the magnitude of these is contingent on the sales that the drug achieves.

69 www.imshealth.com/portal/site/imshealth/menuitem.a953aef4d73d1ecd88f611019418c22a/?vgnextoid=bb967900b55a5110VgnVCM10000071812ca2RCRD&vgnextfmt=default (accessed 27 December, 2009).

70 Richards, W.G. (2009). *Spin-Outs: Creating Business from University Intellectual Property*. Hampshire, UK: Harriman House.

71 Thangaraj, Harry, et al. (2009). "Dynamics of Global Disclosure through Patent and Journal Publications for Biopharmaceutical Products." *Nature Biotechnology* 27 (7): 614–18.

72 Kneller, R. (2010). "The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs." *Nature Reviews of Drug Discovery* 9: 867–82

73 Kneller, R. (2005). "The Origins of New Drugs." *Nat Biotech* 23 (5): 529–30.

74 www.gao.gov/new.items/d03829.pdf (accessed 28 December, 2009).

75 http://pubs.acs.org/cen/news/8222/8222notw2.html (accessed 13 February, 2010).

76 See "A Plan to Ensure Taxpayers' Interests are Protected," July 2001 (www.ott.nih.gov/policy/policy_protect_text.html).

77 See, for example, William F. Swiggart, "The Bayh-Dole Act & the State of University Technology Transfer in 2003," a Panel Presentation at the 4th Annual Conference, Princeton Entrepreneurs' Network, Campus of Princeton University (May 29, 2003; available at www.swiggartagin.com/articles/Bayh_Dole_act.doc; last accessed 21 February, 2015), showing $5 billion in tax impact at the federal, state and local levels when total university royalty income was $850 million.