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Research

The Role of Public-Sector Research in the Discovery of Drugs and Vaccines

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Historically, there has been 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 research institutions (PSRIs) have performed the upstream, basic research to elucidate the underlying mechanisms and pathways of disease and identify promising points of intervention, whereas corporate researchers have performed the downstream, applied research to discover drugs that can be used to treat diseases and have then carried out the development activities to bring the drugs to market. The intellectual property that protects the investment in developing these drugs is created in the applied-research phase.

An excellent example of this traditional approach was Julius Axelrod's research at the National Institutes of Health (NIH) regarding the basic mechanisms of neurotransmitters, for which he received the Nobel Prize in 1970. This research provided the foundation for the pharmaceutical industry's discovery of an entirely new class of drugs, the selective serotonin-reuptake inhibitors (SSRIs), which have been important in the treatment of depression. All the major SSRIs were discovered by pharmaceutical companies with the use of Axelrod's basic discoveries and are therefore not included in our study (e.g., Eli Lilly's discovery of fluoxetine [Prozac], which received approval from the Food and Drug Administration [FDA] in 1987). However, Richard and Judith Wurtman at MIT discovered the role of these drugs in the treatment of premenstrual dysphoric disorder and obtained a method-of-treatment patent for this new use. MIT licensed their work to Interneuron Pharmaceuticals, which later licensed it to Eli Lilly. Eli Lilly then received FDA approval for a new use of fluoxetine and created a separate product, Sarafem, for this new use. Thus, we have included Sarafem in our study.

There is little dispute about the importance to drug discovery of basic research at PSRIs under the traditional approach. Studies by Cockburn and Henderson¹ showed the complex relationships between public and private research in the pharmaceutical industry. Zycher et al.² found that at least 80% of 35 major drugs that they studied were based on scientific discoveries made by PSRIs, whereas Toole³ found a quantifiable correlation between investment in publicly funded basic research and corporately funded applied research: an increase of 1% in the funding of public basic research led to an increase of 1.8% in the number of successful applications for new molecular entities (compounds that have not been approved for marketing in the United States)⁴ after a lag of about 17 years. He found that a \$1 investment in public-sector basic research yielded \$0.43 in annual benefits in the development of new molecular entities in perpetuity.

Historically, PSRIs did not play a major role in the downstream, applied phase of drug discovery, in which the actual products are discovered and patented. However, in the mid-

1970s, the newly emerging tools of biotechnology — recombinant DNA and monoclonal antibodies — allowed PSRIs to create and patent biologic drug candidates and discover and patent small-molecule drugs. At that time, all products created in academic institutions were owned by the government, which granted only nonexclusive licenses. This system resulted in the ineffective transfer of academic technologies.^{5,6} For instance, by 1978, the government had licensed less than 5% of the 25,000 to 30,000 patents it owned.^{7,8}

In 1980, Congress passed two pieces of legislation that transformed the ownership, management, and transfer of intellectual property that is created by PSRIs. First, the Bayh–Dole Act (Public Law 96-517) allowed universities, nonprofit research institutes, and teaching hospitals to own the intellectual property resulting from federally funded research and to license it according to terms of their choosing. Second, the Stevenson–Wydler Technology Innovation Act (Public Law 96-480), as amended by the Federal Technology Transfer Act of 1986 (Public Law 99-502), provided a corresponding authority to federal laboratories.

Under this new approach, inventions that arose from PSRIs, in addition to being freely published in the scientific literature, could also be converted into intellectual property and transferred through license agreements to the private sector for commercialization and public use. The new approach is thought to be considerably more effective than government ownership of academic inventions^{9,10} and was introduced just as the fruits of the biotechnology revolution started to emerge.

Our objective in this study was to quantitate the contribution of public-sector research to the applied-research phase of drug discovery. Other investigators have addressed this issue previously, using a variety of approaches and definitions. Zycher et al.² found that of the 35 drugs they studied, only 1 (3%) originated from PSRIs. DiMasi et al.¹¹ found that of the 284 new drugs approved in the United States from 1990 through 1999, only 6.7% originated from sources other than private industry, whereas Kaitin et al.¹² found that only 7.6% of new drugs approved from 1981 through 1990 originated from nonindustry sources. Sampat¹³ examined listings of patents that protected approved drugs in the Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book,¹⁴ published by the FDA, and identified 60 new molecular entities that originated from public-sector research, resulting in the filing of 72 new-drug applications; however, the author did not relate this number to total approvals during the period of his study. Kneller¹⁵ examined new molecular entities and new biologic molecules receiving FDA approval between 1998 and 2007 and found that 24.1% originated from PSRIs.

METHODS

Definitions

In this study, we have used the term PSRI in a broad sense to include all universities, research hospitals, nonprofit research institutes, and federal laboratories in the United States. We have used the term “drug” to refer to any product that received U.S. marketing approval after 1962 from either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) of the FDA. We have therefore included small-molecule drugs, protein-based biologic drugs, vaccines, and in vivo diagnostic materials.

We considered a PSRI to have participated in the applied phase of research that led to discovery of a drug if it, solely or jointly, created intellectual property specific to the drug that was subsequently transferred to a company through a commercial license. In most cases, the

intellectual property was a patent or patent application. However, a few products have used proprietary biological materials developed and licensed by the PSRI.

We classified patents into six categories according to the following definitions: screening, a way of detecting the existence of a condition either *in vitro* or *in vivo* and of identifying a molecule that is pharmacologically active against the condition; the method of synthesis, 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 composition of matter, a pharmacologically active molecule, or family of molecules, contained in the marketed drug, including peptides, proteins, and the specific DNA sequences used to produce them; the method of treatment, a way of treating a specific condition with the use of a pharmacologically active molecule; the formulation, a way of delivering a compound or of preparing a pharmacologically effective combination of compounds but not the composition of matter of the pharmacologically active compounds that make up the combination; and a medical device, an instrument or apparatus that does not depend on a chemical action or metabolism for the achievement of its primary intended purposes.

We excluded the role of PSRIs in the development of platform technologies that have contributed to the development of whole new classes of drugs, such as recombinant DNA technology (Cohen–Boyer patents), bacterial production methods for recombinant DNA (Riggs–Itakura patents), production and chimerization methods for antibodies (Cabilly patents), methods to produce glycosylated recombinant proteins in mammalian cells (Axel patents), and methods of gene silencing with the use of small interfering RNAs (Mello–Fire patents). Although these platform technologies enabled the development of a large number of products (e.g., the Cabilly patents are used in the production of all antibody drugs), we excluded them because the PSRI scientists who developed the platforms generally did not use them to develop specific drug candidates, and therefore, the platform technologies were generally licensed nonexclusively (i.e., in a way that did not confer any protection of the investment in the development of the marketed drug) at relatively low royalty rates.

Our study encompasses a broad range of relationships. In some cases, the PSRI made the initial discovery independently and subsequently licensed it to the company that developed the drug. In other cases, the relationship started with a public–private collaboration, and the initial patents are jointly owned by the PSRI and its corporate partner, which generally obtained a license to the PSRI’s undivided interest in the patent. Sometimes, simultaneous inventions in the public and private sectors resulted in interference proceedings, which were resolved through negotiation rather than through the patent office. In a few cases, the company that developed the drug did not respect the PSRI’s intellectual property and litigation ensued, ending in the judicial imposition of a license.

Data Sources

There has been no systematic collection of the details of individual transfers of technologies invented by PSRIs. Since 1991, the Association of University Technology Managers has conducted an annual licensing survey¹⁶ that provides aggregate statistics on the outcomes of technology-transfer activities of academic institutions, but the specific technologies, the licensees, and the success or failure of the licensee’s development efforts are not identified. We therefore created a database of successful drug-discovery and drug-development projects that owe their origin, at least in part, to PSRI inventions. The most difficult task was to identify which drugs originated in PSRIs.

Our primary source was the FDA’s Orange Book, which contains details of the patent protection underlying drugs that have received approval under new-drug applications but not

under biologics license applications. If any patent that is listed in the Orange Book is assigned to a PSRI, it is highly likely that the drug originated at that PSRI.

We augmented the Orange Book with a number of sources: collections of stories of specific technology-development projects, including accounts of drug development published by the Association of University Technology Managers; the Web site of the University of Virginia Patent Foundation,¹⁷ which contains a substantial number of success stories of academic licensing; announcements by specialized financial firms¹⁸⁻²⁰ that purchase the right to receive royalty streams from academic institutions or their inventors; lawsuits; and newspaper articles. As a final check, we sent the list of products we had identified to the directors of offices of academic technology licensing. They identified nine additional drugs that their institutions had discovered and licensed.

The second step in our research was to search the database of the Patent and Trademark Office for the patents that protected each product.²¹

Next, we determined as much as possible about each development project. The rDNA database of Recombinant Capital,²² primarily derived from filings of the Security and Exchange Commission, allowed us to trace the various transactions that drugs passed through on their way from discovery to market.

Our final primary source was the FDA's databases for drug²³ and biologic²⁴ approvals. For each product (whenever possible), we identified principal investigators or lead inventors and their institutions; the funding source and dates of any federal grant; the date of the earliest patent application cited in the issued patents; the date, identity, and terms of the initial licensee; 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, both before and after FDA approval; the dates of FDA approval of all new-drug and biologics licensing applications incorporating that active ingredient; and for small-molecule drugs, the FDA chemical classification, whether the product received standard or priority review, and whether it received orphan-drug designation.

RESULTS

Number of Products

Our research has so far identified 153 FDA-approved drugs that were discovered at least in part by PSRIs during the past 40 years (Table 1 in the [Supplementary Appendix](#), available with the full text of this article at NEJM.org). We excluded drugs such as thyroxine, warfarin, nystatin, streptomycin, neomycin, and 5-fluorouracil because these drugs were discovered and introduced before the Kefauver–Harris Amendment (Drug Efficacy Amendment) of 1962, which ushered in the modern era of FDA regulation of drug approvals. Because our sources were not limited to products for which a public-sector patent was listed in the Orange Book, we identified 102 new molecular entities (including 8 in vivo diagnostic materials and 1 over-the-counter product) for which a total of 161 new-drug applications were approved. We also identified 36 biologic drugs and 15 vaccines that received approval under biologics license applications, for a total of 153 drugs that received 206 new-drug or biologics license applications.

Types of Products

We identified the distribution of the 153 products among four broad categories of therapeutic products (Table 1 in the [Supplementary Appendix](#)). Particularly noteworthy was the large

number of vaccines. Virtually all the important, innovative vaccines that have been introduced during the past 25 years have been created by PSRIs.

Therapeutic Categories

Therapeutic Area	Number
Total	153
Hematology or oncology	40
Infectious disease	36
Cardiology	12
Metabolic disease	12
Central nervous system	12
Dermatology	7
Renal disease	7
Ophthalmology	6
Immunology	6
Gastroenterology	4
Women's health	3
Allergy	2
Pulmonary disease	2

Table 1: Number of Drug Products Approved by the Food and Drug Administration and Originating from Public-Sector Research, According to Therapeutic Area, 1970–2009.

Discovers through Public-Sector Research, According to Type of Review and CI						
New Molecular Entity	New Ester, Salt, or Derivative	New Formulation	New Combination	New Manufacturer	No. Drugs	No. PSR
44	1	17	3	8	73	1
208	8	88	33	14	342	1
21.1	16.7	13.2	11.8	8	60	9
28	0	36	8	7	79	1
174	11	102	98	137	522	11
7.3	0	5.7	6.2	5.1	24.3	8
84	2	53	9	7	155	1
481	39	708	116	151	1485	13
13.3	1.8	5.3	7.8	4.6	32.8	8

of PSR (public-sector research) initiation: none approved for Pfizer's Sildenafil in 2006, was classified as type II (new indication by the FDA allowed) no priority reviews for new-indication applications in 2006 or 2007.

Table 2: FDA-Approved Drugs Discovered through Public-Sector Research, According to Type of Review and Chemical Type, 1990–2007.

The therapeutic categories into which the 153 products fall are shown in Table 1. Oncology and infectious diseases account for half the total. The order of these disease categories is very different from the priorities of the pharmaceutical industry. The disease priorities of the NIH institutes with the largest budgets²⁵ — in order, the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, and the National Institute of Diabetes and Digestive and Kidney Diseases — broadly correlate with the top four categories of PSRI-discovered drugs (Table 2). One possible interpretation of this observation is simply that there was more funding available for research involving these disease categories, which resulted in more useful intellectual property.

Discovering Institution and Rate of Discovery

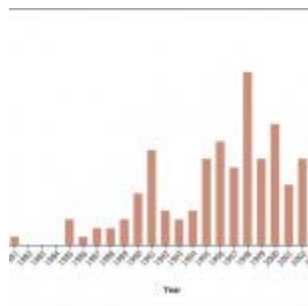


Figure 1: Year of Approval of All New-Drug and Biologics License Applications. shows the number of new-drug and biologics license applications approved by the FDA each year.

A total of 75 PSRIs discovered or codiscovered at least one product (Table 1 in the **Supplementary Appendix**). Of these institutions, the most prolific is the NIH (with 22 products), followed by the University of California system (with 11), Memorial Sloan-Kettering Cancer Center (with 8), Emory University (with 7), and Yale University (with 6).

Clinical Effect of PSRI Drugs

The FDA-approval process provides two indications of the clinical significance of a new drug. The FDA classifies new-drug applications into one of eight chemical types: type 1, a new molecular entity; type 2, a new ester, salt, or other noncovalent derivative; type 3, a new formulation; type 4, a new combination; type 5, a new manufacturer; type 6, a new indication; and type 7, a drug that is already marketed but does not have an approved new-drug application.

The FDA assigns the application one of two types of review on the basis of its therapeutic potential: priority review if the drug shows substantial improvement, as compared with currently marketed products for the treatment, diagnosis, or prevention of a disease, or standard review if the drug appears to have therapeutic qualities similar to those of one or more drugs that are already on the market. A drug that has been designated as a new molecular entity and that has received a priority review would therefore be considered by the FDA to have the highest potential therapeutic effect.

We obtained the total number of approvals of new-drug applications, according to chemical type and type of review, for the 18-year period from 1990 through 2007 from the FDA's Web site²⁶ and by a request under the Freedom of Information Act. During this period, the FDA approved 1541 new-drug applications but granted priority review to just 348 applications (22.6%) (Table 2). Of the 1541 total approvals, 143 (9.3%) resulted from PSRIs. However, of the 348 priority reviews, 66 (19.0%) resulted from PSRIs, or twice the overall rate for priority reviews. Viewed from another perspective, 46.2% of new-drug applications from PSRIs received priority reviews, as compared with 20.0% of applications that were based purely on private-sector research, an increase by a factor of 2.3.

Of the total approvals of new-drug applications, 483 (31.3%) were for new molecular entities, of which 64 (13.6%) originated at PSRIs. Of these new molecular entities, 209 (43.3%) received priority review during this period; of these, 44 (21.1%) came from PSRIs.

The largest category of new-drug applications was for new formulations, with 730 of total approvals (47.4%); of these, 53 (7.3%) originated in PSRIs. Of the new formulations, 99 (13.6%) were considered to have sufficient therapeutic importance to receive priority review; of these, 17 (17.2%) originated in PSRIs.

A total of 116 approvals of new-drug applications (7.5%) were for new drug combinations; of these, 9 (7.8%) originated in PSRIs. Of the new drug combinations, 20 (17.2%) were considered to have sufficient therapeutic importance to receive a priority review; of these, 3 (15.0%) originated in PSRIs.

Drug manufacturers file most applications for new indications of approved drugs as an efficacy supplement to the existing new-drug application rather than as a separate application. A large number of such supplements are filed every year. Only 10 approvals of new-drug applications (0.6% of the total) were for new indications, but 9 (90%) originated in PSRIs.

Thirty-nine of the products received an orphan-drug designation, indicating that the drugs addressed conditions that affected fewer than 200,000 patients.

DISCUSSION

We believe that our data set is more comprehensive than those developed by previous investigators in part because we sought the input of the officers responsible for managing intellectual property for PSRIs. In addition, we did not limit ourselves to intellectual property listed in the Orange Book. However, we cannot be sure that our data are truly comprehensive.

We also did not set out to comprehensively identify the intellectual property generated by the companies that developed the drugs that augmented the intellectual property licensed from the PSRIs. Thus, our data identify drugs that were discovered in whole or in part at PSRIs.

We believe that our study supports the concept that the emergence of biotechnology in the mid-1970s, combined with policy changes implemented in the early 1980s regarding the ownership and management of the intellectual property of PSRIs, allowed these institutions to play an important role in the downstream, applied phase of drug discovery. Our data show that PSRIs have contributed to the discovery of 9.3 to 21.2% of all drugs involved in new-drug applications approved during the period from 1990 through 2007. These proportions are higher than those identified by some earlier researchers. Our data also suggest that PSRIs tend to discover drugs that are expected to have a disproportionately important clinical effect.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://nejm.org).

Source Information

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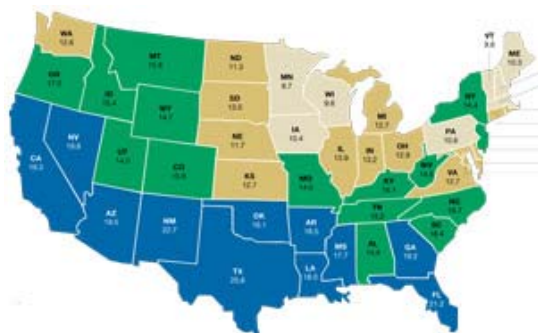
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