

Subtheme: 6.1

**The Contribution of Public Sector Research outside the US to the  
Discovery of New Drugs and Vaccines**

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## **Abstract**

In a companion article, we analyzed the role of public-sector research in the discovery of drugs and vaccines in the US. There has hitherto been no comparable research on the contribution of public-sector research institutions (PSRIs) to the discovery of new drugs and vaccines outside the US. Identifying drugs discovered by PSRIs' from eleven countries, this paper investigates the contribution of PSRIs outside the US to pharmaceutical innovation.

We found that during the past 40 years, 48 new approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out in whole or in part by PSRIs outside the US. These drugs included 34 new chemical entity, 9 biologic drugs and 5 vaccines. More than 70% of these drugs have been used in the treatment or prevention of cancer or infectious diseases.

Although PSRIs outside the US made a great contribution to new drug discovery, the number of drugs they discovered is substantially lower than those discovered by US PSRIs in the same period. One possible explanation for this difference is that the US technology transfer model was not in place in most of these countries for the majority of the drug study period. Another important related factor may be the levels of public funding for academic biomedical research in these countries are substantially less than in the US.

**Keywords:** Public sector research; New drug and vaccine; non-US countries

## **1. 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, in the past few decades there has been a dramatic change in the roles of the public and private sectors in the discovery of new drugs. Since the dawn of the biotechnology era in the US and the UK in the mid 1970's, the public sector has had a much more direct role in the applied research phase of drug discovery than has been 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 these same two countries' legal frameworks governing the ownership, management and transfer of the intellectual property resulting from public sector research.

The contribution of PSRIs to the discovery of new drugs and vaccines has previously been examined by several researchers. Studies by Cockburn and Henderson (1997) suggested that public sector research plays an important role in the discovery of new drugs, but also showed the complex interrelationships between public and private research in the pharmaceutical industry. Angell (2004) 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. Zycher and DiMasi (2008) have shown that upwards of 80% of drugs are based on basic scientific discoveries made in the public sector, while Toole (2010) 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 previously been approved for marketing in the United States) 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. Tralau-Stewart and Wyatt (2009) focus on the new models of pharmaceutical industry research, notably involving academia as a ‘front end’.

In a companion article (Stevens et al., 2011), we show that over the past 40 years, 153 new US Food and Drug Administration (FDA)<sup>1</sup> approved vaccines, drugs and/or new indications for existing drugs were created during the course of research carried out in PSRIs. Public-sector research has had a more immediate effect on improving public health than was previously realized.

There has hitherto been no comparable research on the contribution of PSRIs outside the US to the discovery of new drugs and vaccines. We have found that PSRIs in countries such as the United Kingdom (“UK”), Canada, Israel, Germany, France, the Czech Republic, Belgium, Australia, Japan, Switzerland and India have also made significant contributions to new drug discovery. The environment of PSRIs for research and development (R&D) on new drugs and vaccines varies in different countries.

In this article we analyze the contribution of PSRIs in these different countries. The institutions where the discoveries occurred are identified. More specifically, this study identifies the detailed timeline of the development programs, from the actual discovery of the drug to the initiation of development and finally to approval by the FDA, the European Medicines Agency (EMA)<sup>2</sup> or corresponding governmental agency in an individual country. We analyze the complex, multi-step development pathways that brought these discoveries to a successful conclusion with market

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<sup>1</sup> US Food and Drug Administration: <http://www.fda.gov/>

<sup>2</sup> European Medicines Agency: <http://www.ema.europa.eu>

introduction.

The rest of the paper adopts the following organization. In section 2 we outline the data sources and methodologies involved in our studies. In section 3, we analyze our data and present the results. Concluding remarks and policy recommendations for public sector, university and government policymakers are found in section 4.

## **2. Data and Methodology**

### **2.1 Definitions**

In this study, we use the term “public sector research institutes” or PSRIs, in a broad sense to include all universities, research hospitals, nonprofit research institutes, and national laboratories. In this paper we primarily focus on PSRIs in countries other than the US. We also include the not-for-profit Public–Private Partnerships (PPPs), also known as non-governmental organizations (NGOs), the non-profit drug development companies that have been created mainly since 2000 to achieve a public health objective or to develop a health-related product or service, primarily in the developing world (Farrugia et al., 2008). They raise funding from philanthropic, governmental and intergovernmental sources to carry out drug R&D. Their goal is to reduce health inequality in developing countries, stimulating research in diseases which are unattractive commercial targets, and facilitating access to vaccines and medicines for populations without purchasing capacity. Examples are the Drugs for Neglected Diseases Initiative (DNDi), the Foundation for Innovative New Diagnostics (FIND), and Medicines for Malaria Venture (MMV) which were established in the last decade to develop and implement new diagnostic tools and improved medicines to fight malaria, tuberculosis, and other neglected diseases. The first products to result from these initiatives are starting to reach the market (Table 1).

#### **Table 1: The Public–Private Partnerships and their first products**

We use the term “drug” to refer to any product that received marketing approval

from FDA or EMA or from an individual country government agency which is responsible for drug approval. We therefore included small-molecule drugs (including novel fixed dose combination therapies (FDCT), protein based biologic drugs, vaccines, and in vivo diagnostics materials.

In the UK, drug to be sold must be approved by the Medicines and Healthcare products Regulatory Agency (MHRA)<sup>3</sup>. Similarly, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)<sup>4</sup> is responsible for approving drugs for sale in France, the Bundesinstitut für Arzneimittel und Medizinprodukte (BFARM)<sup>5</sup> is in charge of product approvals in Germany the Státní Ústav pro Kontrolu Léčiv (SUKL)<sup>6</sup> is responsible for drug approvals in the Czech Republic and so forth.

In 1995, the European Union (EU) established the European Medicines Evaluation Agency (EMEA) now called the European Medicines Agency (EMA), headquartered in London, which is responsible for the scientific evaluation of medicines for use throughout the European Union. Therefore, after 1995, drugs to be licensed for use in European Union can be approved by either the EMA or the individual country's government agency. For example, to be marketed in Belgium, drugs must be registered with the General Pharmaceutical Inspectorate (GPI) in Belgium or with the EMA.

In Canada, Health Canada approves drugs for marketing in Canada and lists them in their Drug Product Database (DPD)<sup>7</sup>. The Israeli Ministry of Health (IMH)<sup>8</sup> is responsible for the drugs in Israel. In Japan, there were three major agencies (Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), Organization of Pharmaceutical Safety and Research (OPSR) and the Japan Association for the Advancement of Medical Equipment (JAAME)) responsible for drug and medical device approval, which merged into one organization called the Pharmaceuticals and

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<sup>3</sup> Medicines and Healthcare products Regulatory Agency: <http://www.mhra.gov.uk/index.htm>

<sup>4</sup> French Health Products Safety Agency: <http://www.afssaps.fr/>

<sup>5</sup> Federal Institute for Drugs and Medical Devices: [http://www.bfarm.de/EN/Home/home\\_node.html](http://www.bfarm.de/EN/Home/home_node.html)

<sup>6</sup> State Institute for Drug Control : <http://www.sukl.cz/medical-devices-1?lang=2>

<sup>7</sup> Health Canada Drug Product Database : <http://www.hc-sc.gc.ca/index-eng.php>

<sup>8</sup> Israeli Ministry of Health : [http://www.health.gov.il/english/Pages\\_E/default.asp](http://www.health.gov.il/english/Pages_E/default.asp)

Medical Devices Agency (PMDA)<sup>9</sup> in 2004. The Central Drugs Standard Control Organization (CDSCO)<sup>10</sup> is responsible for drug approval in India.

We consider a PSRI to have participated in the applied phase of research that led to discovery of a drug if the PSRI, either 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.

We excluded the role of PSRIs in the development of platform technologies that have contributed to the development of whole new classes of drugs. We excluded them because the PSRIs scientists who developed the platforms generally did not use them to develop specific drug candidates, and therefore, the platform technologies were generally licensed nonexclusively at relatively low royalty rates. 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 (including novel combinations) which was licensed by the PSRI to the corporate developer of the technology.

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 undivided interest in the patent.

## **2.2 Data sources**

The initial list of new drugs analyzed in this study was obtained from the FDA website, the EMA website and diverse other sources. As discussed in more detail below, the most difficult task was to identify which drugs originated in PSRIs.

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<sup>9</sup> Pharmaceuticals and Medical Devices Agency : <http://www.pmda.go.jp/english/index.html>

<sup>10</sup> Central Drugs Standard Control Organization : <http://cdsco.nic.in/listofdrugapprovedmain.html>

A primary source of information was the FDA's Orange Book<sup>11</sup>, 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<sup>12</sup>, which contains a substantial number of success stories of academic licensing; announcements by specialized financial firms that purchase the right to receive royalty streams from academic institutions or their inventors; newspaper articles and personal communications. For the not-for profit PPPs, we checked their websites to see if they had received marketing approval for specific drugs. As a final check, we sent the list of products we had identified to directors of academic technology licensing offices worldwide to identify drugs we had missed.

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. Some natural products such as  $\alpha$ -interferon, was discovered by Alick Isaacs, a virus researcher at the UK Medical Research Council (MRC) in May 1958. It was so difficult to isolate  $\alpha$ -interferon from natural sources that the MRC was not able to identify effective uses of it and their discovery was not commercialized, though when recombinant DNA techniques two decades later allowed copious production of  $\alpha$ -interferon, its efficacy in the treatment of hepatitis B and C and certain cancers was discovered and recombinantly produced interferon is now a major drug. However, the MRC's IP was not required for the commercialization of recombinant  $\alpha$ -interferon and therefore  $\alpha$ -interferon is not

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<sup>11</sup> Orange Book: approved drug products with therapeutic equivalence evaluations. Silver Spring, MD: Food and Drug Administration. <http://www.fda.gov/cder/ob>

<sup>12</sup> University of Virginia Patent Foundation: <http://uvapf.org/>

included in our study.

By contrast, Sidney Pestka and Menachem Rubinstein at the Weizmann Institute of Science (WIS) in Israel obtained patents on naturally-derived  $\beta$ -interferon and Serono received marketing approval for naturally produced  $\beta$ -interferon under the tradename Frone in Italy in the mid 1980's for viral diseases and cancers. A recombinant version of  $\beta$ -interferon drug, interferon beta-1a, was discovered by Michel Revel at WIS and Serono received FDA approval for treatment of multiple sclerosis in 2002 under the tradename Rebif. Because WIS licensed both drugs to Serono, we have included both Frone and Rebif in our study.

Overall we identified 48 new drugs from eleven countries and not-for-profit PPPs. These drugs are divided into three groups (Table 2).

### **Table 2: Three groups of the PSRIs drugs**

The first group contains 17 drugs which received approval from the FDA for US sale and were co-discovered by US and non-US PSRIs, i.e, both US and non-US public sector researchers made a contribution to the discovery of the drug. Sixteen of those 17 drugs were included in our companion article on the role of US PSRI's in drug discovery. One of these drugs wasn't included in our US drug study, Coartem, an FDCT to treat malaria which was developed by Medicines for Malaria Venture (MMV), one of the public-private partnerships discussed above. This category of PSRI was not included in the US study.

The second group contains 19 drugs which are discovered entirely by non-US institutions and approved by the FDA which means these drugs can be sold in the US.

The third group contains 12 drugs which were discovered by non-US PSRIs and have not yet been approved by FDA for US sale but have been approved by the EMA or one or more individual government agencies. Examples include, Myocet, discovered by the University of British Columbia and approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide, and Bio-Hep-B (hepatitis B vaccine) was approved by the Israel Ministry of Health in 2000.

After we identified drugs that had resulted from PSRIs, the second step in our study was to search the database of the Patent and Trademark Office for the patents that protected each product. However, most drugs developed so far by PPP's are novel combinations of compounds that are unpatented or whose patents have expired. Our primary source of data here was the United States Patent and Trademark Office (USPTO)<sup>13</sup> database. 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, ReCapIP<sup>14</sup>, and conducted internet searches, which would yield hits such as FDA patent term extension dockets or marketing websites dedicated to a particular drug.

The third step in our research was to determine as much as possible about how each drug was developed. The IQ Series by Deloitte database<sup>15</sup> (formerly 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. For drugs that we could not track through found in the IQ Series by Deloitte database, we contacted the inventor or their PSRI to ask for details of the commercialization process.

The fourth step in our research was to obtain information on the drug's approval process from the FDA's drug<sup>16</sup> and biologic<sup>17</sup> approval databases, and/or the EMA and individual country government agency databases.

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<sup>13</sup> United States Patent and Trademark Office : <http://www.uspto.gov/patents/process/search/index.jsp>

<sup>14</sup> RECAP by Deloitte home page. <http://www.recap.com>

<sup>15</sup> The IQ Series by Deloitte database :  
<http://www.recap.com/88256afe0004abf3/iqhomerecap?openform>

<sup>16</sup> Drugs@FDA home page. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.

<sup>17</sup> Vaccines, blood & biologics. Silver Spring, MD: Food and Drug Administration. <http://www.fda.gov/Biologics/BloodVaccines/default.htm>.

### 3. Results

#### 3.1 Number of Products

We found that during the past 40 years, 48 new approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out by PSRIs outside the US. These drugs consisted of 34 new chemical entity, 9 biologic drugs and 5 vaccines. For each product, we attempted to identify the principal investigators or lead inventors and their institutions; the dates of the grants; 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 sub-licensees or assignees during the course of bringing the product to market, both before and after approval; the dates of approval of all new-drug and biologics licensing applications incorporating that active ingredient.

Overall, a total 48 drugs were discovered or co-discovered by PSRIs in eleven different countries and PPPs. We credit all of a PPP's successfully developed drugs to the country in which they are headquartered. For example, we attribute the three drugs successfully developed by DNDi to Switzerland, even though DNDi was established by seven organizations from round the world: five PSRIs – the Oswaldo Cruz Foundation in Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France's Pasteur Institute; one humanitarian organization, Médecins sans Frontières (MSF); and one international research organization, the UNDP/World Bank/WHO's Special Program for Research and Training in Tropical Diseases (TDR).<sup>18</sup>

Of these eleven countries, the most prolific is the UK, which contributed 10 drugs, followed by Canada with 9 products and Israel, with 7 products. These three countries account for 56.3% of the total. France discovered 4 products. Australia and Germany each separately contributed 3 products, and co-discovered 1 product. The Czech

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<sup>18</sup> Drugs for Neglected Diseases initiative (DNDi): <http://www.dndi.org/index.php/overview-dndi.html?ids=1>

Republic and Belgium (CR/B) jointly discovered 3 products. Japan and India each discovered 2 products.

The PPPs together contributed 6 drugs. Were they a separate country, they would have been the fifth most prolific. Of these 6 drugs, 4 products were discovered in Switzerland and 2 products were discovered in the US. As noted above, in this study, we mainly focus on the countries other than the US, so we exclude the two drugs developed by Program for Appropriate Technology in Health (PATH)<sup>19</sup> and Institute for One World Health (IOWH)<sup>20</sup>, as their headquarters are in the US. Among the 4 drugs in Switzerland, three drugs are attributed to DNDi, one drug is from MMV (Figure 1).

### **Figure 1. Countries Distribution of all PSRIs' new drugs**

These not-for-profit organizations today play a major role in improving global health. The global burden of disease, especially the part attributable to infectious diseases, disproportionately affects populations in developing countries. According to the WHO, worldwide, these groups of neglected diseases affect about 1 billion people (roughly 15% of the world's population). Therefore, there is a tremendous need to develop and deliver effective therapies for these neglected diseases. PPPs are an effective solution to this need. Taking the FDCT drug ASAQ, which now is registered in 24 African countries and India, as an example, there were over 20 million malaria episodes being treated in 2009. This is the most ambitious proactive drug monitoring program ever launched in Africa, for any drug.

## **3.2 Therapeutic Categories**

We classified the specific indications for each drug. The therapeutic categories into which the 48 products fall are shown in Table 2. There are 20 drugs for infectious diseases, accounting for 41.7% of the total and 17 drugs for hematology/oncology, accounting for 35.4% of the total. This distribution of new products is very different

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<sup>19</sup> PATH: <http://www.path.org/>

<sup>20</sup> Institute for One World Health (IOWH): <http://www.oneworldhealth.org/>

from the distribution of new products developed by the pharmaceutical industry (Table 3).

### **Table 3: Therapeutic Categories of Products**

As show in figure 2, of the 10 drugs which are invented by the UK, there are 7 hematology/oncology drugs. The UK has two long-standing, highly effective cancer research organizations that receive extremely generous donations from the public, the Imperial Cancer Research Fund and the Cancer Research Campaign, which merged in 2002 to form Cancer Research UK. Cancer Research UK is credited with 4 cancer drugs. Canada has 6 drugs to treat infectious diseases out of a total of 9 drugs. Of the 6 infectious disease drugs, 5 were discovered by McGill University and the Institute Armand-Frappier. All the drugs from the Switzerland, Czech Republic, Belgium and India are to treat infectious disease, all the drugs invented in Germany are for hematology/oncology.

### **Figure 2. Distribution of Therapeutic Categories in Countries**

### **3.3 Initial Developing Companies and Marketing Companies**

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

1. Large company, a company with more than 500 employees;
2. Small company, a company with fewer than 500 employees;
3. Start-up, a company formed specifically to develop the technology/drug, and a special case of a small company.

The distribution of licensees between these three categories is shown in Figure 3. We classified the company according to its status when the license was executed. For instance, today Gilead is clearly a large company, with over 4,000 employees worldwide. However, when Gilead licensed Hespera from the Czech Academy of Sciences and the Catholic University in Leuven in 1991, it was not a big company. When Gilead licensed Viread in 1996, it had already made the transition to a large

company with more than 500 employees, and is so classified in our study.

Some 37 different companies initially received licenses to the PSRIs' discoveries. Small companies (including the category of start-up companies which were specifically founded to develop the drug) constituted 39.6% of the companies which initiated development of the drug. The percentage of licenses with large companies is 60.4% (Figure 3), significantly higher than both that typically reported in the AUTM Annual Survey<sup>21</sup>, where the percentage of licenses with large companies was 35.1% in 2008, and also higher than the initial licensees of the US PSRI discovered drugs, where the percentage of licensees with large companies was 42.5%. 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.

### **Figure 3: Initial Developing Companies**

The distribution of initial developing companies by country is shown in Figure 4. In most countries, large companies licensed the overwhelming majority of the drugs, followed by small companies and the percentage of licensees with start-up companies is lowest. For example, in the UK, the percentage of licensees with large companies was 70%, in the Czech Republic/Belgium it was 66.7%, in Canada it was 55.6%. In Switzerland and Japan, the percentage was 100%. The most notable exception is Germany and France where start-up companies licensed half of the drugs.

### **Figure 4. Distribution of Initial Developing Companies in countries**

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; there is only one exception which the initial large company licensee gave the technology back to the university and it was relicensed to a start-up. Campath was initially licensed by British Technology Group (BTG) which marketed technologies for Cambridge University, to The Wellcome Foundation, who subsequently terminated the license. In

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<sup>21</sup> Association of University Technology Managers. [http://www.autm.net/about/dsp.licensing\\_surveys.cfm](http://www.autm.net/about/dsp.licensing_surveys.cfm)

June 1996, BTG licensed rights to Campath to LeukoSite Inc., a Harvard spin-out that had been formed in 1994. In 1999, Millenium Pharmaceuticals acquired Leukpsite for \$635 million.

When the licensee is a small company or a spin-out company, the licensor generally expects that 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. 33 different companies are currently marketing the 48 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. GlaxoSmithKline sells the most drugs that originated in public sector research, with 7 drugs, followed by Novartis, with 4 drugs, Gilead, Bristol-Myers Squibb and Sanofi-Aventis each sell 3 drugs, followed by Merck, Pfizer, Serono which each sell 2 drugs. However, it is noteworthy that 15 of the products are marketed by 13 biotechnology companies which were 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. For instance, Tomudex was initially licensed to Zeneca in 1996 which was merged with Astra AB to form AstraZeneca in 1999, and then transferred the license to Hospira, which was a new company spun out of Abbott Laboratories in 2004.

Some of these drugs have more than one marketer worldwide. For example, Removab is marketed by Fresenius Biotech in Germany and Austria while Swedish Orphan Biovitrum (Sobi) signed a Removab distribution agreement with Fresenius Biotech in 2011 and will distribute Removab exclusively in fifteen European countries over seven years. Myocet also currently has two marketer, Cephalon in Europe and Sopherion Therapeutics in the US and Canada.

### **3.4 Transactions**

There have generally been thought to be two pathways for commercializing academic technologies: one is a one step pathway when the initial licensee is a large

company which develops the technology and takes it to market itself; The other is 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.

However, one of the most surprising findings in our study, confirming similar findings in the companion US study, is that both of these pathways are vast over-simplifications and Table 4 shows how the number of steps in the development pathway varies between the three categories of initial licensee.

**Table 4: Number of Steps of the drugs' Transactions**

As would be expected, where the initial licensee is a large company, a majority of the companies take the products to market themselves and there are no further transactions. However, in 31% 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 monetization of a royalty stream.

In the cases where the initial licensee is a small company, the situation is reversed, with additional transactions in 83.3% of the cases. While 25.0% of the cases were the “classical” two step pathway, 58.3% had more than two steps. There are two products where there are no further transactions and the small company is marketing the product themselves. 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 approval of the product.

The situation is almost the same when the initial licensee was a spin-out company. There are two products, accounting for 28.6%, of the cases, where the spin-out company is marketing the products themselves, while 42.9% of the cases involve a two step pathway and 28.6% of the cases involve three steps.

One of the most complex pathways we identified is that for Campath, a drug for the treatment of chronic lymphocytic leukemia, which was discovered at Cambridge University and involved nine transactions. The complete timeline of Campath's development is as follows:

- A murine Campath antibody was initially licensed in 1985 by British Technology Group (BTG) which had responsibility for licensing the University of Cambridge's IP, to The Wellcome Foundation (which despite its name was a for-profit drug company albeit owned by a non-profit foundation, and which merged with Glaxo in 1995 to form Glaxo-Wellcome and is now part of GlaxoSmithKline);
- The inventor, Herman Waldemann, filed the patent application on Campath-1 in October 1989;
- In 1995, around the time that Wellcome was considering a merger with Glaxo, it announced it was abandoning Campath and gave rights back to Cambridge;
- In 1996, Cambridge University, through its IP ownership company, Lynxvale Ltd., licensed rights to a 2 year old Boston company, LeukoSite. The inventor, Dr. Waldmann, was a consultant to LeukoSite;
- In 1996, LeukoSite and ILEX Oncology formed a joint venture to develop Campath;
- Millennium Pharmaceuticals, Inc acquired LeukoSite for \$635 million in September 1998;
- In 1999, LekoSite and ILEX granted Schering AG marketing rights to Campath in all countries outside certain Far Eastern countries for a \$30 million payment and 67% share of future income and losses. Schering acquired the remaining rights several years later;
- ILEX received FDA approval of Campath for the treatment of B-cell CLL in May 2001;
- In October 2001, Millennium transferred its rights in Campath to ILEX for \$140 million and a royalty on future sales;

- In February 2004, Genzyme Oncology, Inc. acquired ILEX for \$1,000 million and gained the production rights to Campath;
- In June 2009, Genzyme acquired Schering AG's interests in Campath and two other drugs from Bayer AG, which had itself acquired Schering AG, for \$2.9 billion.

The commercialization process of Campath is long and winding, there were nine steps in the pathway, which initially licensed to a large company Wellcome, then to a small company LeukoSite who with ILEX co-developed Campath. Three years later, LekoSite and ILEX granted Schering AG to market Campath in most of the countries. After LeukoSite's merger with Millennium, Campath was transferred to ILEX, which was finally acquired by Genzyme. Finally Genzyme acquired Schering AG's marketing rights to Campath. Finally, when Genzyme was acquired by Sanofi in 2011, alemtuzumab (i.e., Campath) was being developed to treat multiple sclerosis and its potential contribution to future revenues was a major factor in the protracted (~one year) negotiations between the two companies and resulted in a "Contingent Value Rights" structure for the deal in which Genzyme shareholders could receive additional compensation depending on the revenues achieved by alemtuzumab in the multiple sclerosis market.

Using the Deloitte database, we were able to identify 37 additional transactions involving the drugs in our study. As shown in Table 3 and presented graphically in Figure 5, 24 of the 48 products in our database involved only one step in the development pathway, while the remaining 24 products involved at least one additional transaction. Overall, 50% of the development pathways involved only one step, 29% involved two steps and the remaining 21% involved more than 2 steps.

Where a large company was the initial licensee, 20 drugs (69.0%) have one step, 8 drugs (27.68%) have two steps while where small and start-up companies were the initial licensee, 4 drugs (21.1%) involved one steps, 6 drugs (31.5%) involved two steps, and 9 drugs (47.4%) involved more than two steps.

We classified these additional transactions as to whether they occurred before or

after approval of the drug. Of the 37 additional transactions, 16 occurred before approval, while 21 occurred after approval.

### **Figure 5. Distribution of Number of Steps in Commercialization Pathway**

#### **3.5 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. The timelines are highly variable in length and reflect the diversity of the relationships we identified, which, as noted above, were highly diverse: i) collaborative research projects that resulted in discovery of the product; ii) independent academic research that resulted in the discovery which was subsequently licensed to the corporate partner; iii) situations where litigation resulted in an infringement judgment against the developing company and hence acceptance by the developing company of the validity of the PSRIs' patent.

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 initial approval.

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. In this way, we were able to identify a date of discovery for 41 of the products. One product, Frone (natural  $\beta$ -interferon) has no patent but we obtained the discovery date from the inventor. and the products developed by PPPs' to date have generally been novel combinations of compounds on which the patents have expired and for which they do not seek patent protection, so we were unable to determine their discovery date. Equally, two Indian drugs we were unable to identify their discovery date. For example, Immunol, a leprosy drug, developed by National Institute of Immunology in India, has no patent protection because it was on National Requirement Mode. We were able to identify 42 drugs' discovery dates. Therefore, in the following timeline analysis, we only use these 42 drugs as the sample. They are from nine countries.

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.

The date of product approval was obtained from the FDA, EMA or an individual government agency. Most of drugs were initially approved by FDA, but some were initially approved by EMA or other countries. In such cases, we used the earliest approval date. For example, Chugai received Japanese approval for Actemra (a humanized antibody to the IL-6 receptor, which was discovered by Osaka University) in 2005 but the US licensee, Roche, did not receive FDA approval until January 2010. Another drug Exelon, which was invented by Hebrew University of Jerusalem, was approved by EMA in December 1998 but did not receive FDA approval until April 2000.

### **3.5.1 Product Development Timelines**

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 IQ Series by Deloitte 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 technology transfer offices 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. Table 5 presents a overall product development timelines.

### **Table 5: Overall Product Development Timelines**

We were able to determine the date of the start of development for 42 products. The average time of the drugs from discovery to initial license was 2.7 years, with a standard deviation of  $\pm 5.3$  years. The longest prosecution history we found was 15.7 years .

The average time of the drugs from initial license to initial approval was 7.3 years, with a standard deviation of  $\pm 4.8$  years. The longest prosecution history we found was 18.8 years .

The average time of the drugs from discovery to initial approval was 10.1 years, with a standard deviation of  $\pm 4.5$  years. The longest prosecution history we found was 18.7 years.

### **3.5.2 Discovery to Initial Approval**

In Figure 6, we plot the distribution of time from discovery to initial approval. Most of the drugs took from eight to ten years from discovery to approval; two drugs took less than 2 years from discovery to approval and one drug took more than 18 years from discovery to approval.

### **Figure6: Distribution of Time from Discovery to Initial Approval**

In Figure 7, we plot the mean time from discovery to initial approval in the nine countries. In Germany the average time from discovery to initial approval was 13.7 years, the longest of any country, followed by Australia, where the average time was 11.2 years. France has the shortest time from discovery to initial approval, averaging 7.0 years. In our companion article, we found the average time from discovery to initial approval in the US was 11.5 years.

### **Figure7: Mean of Time from Discovery to Initial Approval in countries**

In Figure 8, we plot the distribution of the discovery year of the products. Unlike what we observed in the US, it appears that the number of products discovered each year has been relatively constant at 2-3 drugs through the 1980's, doubling to 6 each

year in 1988 and 1989. Generally, 2 new drugs were discovered in the 1970's, 24 new drugs were discovered in 1980's which is more than half of the total and 15 new drugs were discovered in 1990's.

From 1993 on, the rate of discovery has dropped to around 1 per year, and no drugs have been discovered since 1999. We believe this should not be interpreted as indicating a decline in public sector research productivity, but rather, as we show above, reflecting the long development timelines of public sector discovered drugs. Many of the drugs discovered since the 1988/89 peak are still making their way through the development pipeline.

### **Figure 8 -- Number of Drugs Discovered by Year**

In Figure 9, we plot the number of drugs receiving their initial approval each year. There are 4 drugs approved during 1980's, 20 drugs approved during 1990's, 18 drugs approved from 2000 to 2010.

### **Figure9: Year of initial Approval**

#### **3.6 Proportion and clinical impact of PSRIs Drugs**

We measured the extent of PSRIs contribution using FDA drug approval data. We were able to quantify both the overall extent of the PSRIs' contribution and the clinical significance of the drugs discovered by PSRIs as follows.

The FDA approval process provides two measures of the clinical significance of a new drug. The FDA classifies NDAs, into one of eight chemical types: type 1, a new molecular entity; type 2, a new ester, salt, or other non-covalent 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 also assigns the application one of two types of review based on the drugs' anticipated therapeutic potential: Priority Review, if the drug candidate shows significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease; Standard Review, if the drug appears to have therapeutic

qualities similar to those of one or more already marketed drugs. A drug designated an NME and which received a Priority Review would therefore be considered by the FDA to have the highest therapeutic impact.

Of our 48 PSRIs drugs, there are 36 drugs approved by FDA between 1983 and 2010, 31 drugs approved by FDA during 1990 to 2007. Of these 31 drugs, 16 are new molecular entity; 1 is a new ester; and 5 are new formulation.

In the companion article, 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 Website 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%). However, of the 31 drug resulted from non-US PSRIs, 16 were granted priority review (51.6%). More than twice the overall rate for priority reviews.

Of the total FDA approvals of new-drug applications, 483 (31.3%) were for new molecular entities, of these new molecular entities, 209 (43.3%) received priority review during this period; Of our 31 PSRIs' drugs, 16 (51.6%) were for new molecular entities, of these new molecular entities, 11 (68.8%) received priority review.

#### **4 Conclusions**

In our companion article, we found over the past 40 years that 153 new FDA approved vaccines, drugs and/or new indications for existing drugs were created during the course of research carried out in public sector institutions. In this study, we found 48 new approved drugs or vaccines were invented by non-US public sector institutions during this same timeframe. The number of drugs discovered by non-US PSRIs is substantially less than those discovered by US PSRIs.

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”. The Professor’s privilege model may be automatically vesting ownership in research in a party that

may not be best placed to advance the discovery and may discourage links with industrial partners (to avoid staff leaving to join industry). Some researchers themselves may not be interested in commercialization, but in furthering the research itself. There is no evidence that Professor's Privilege leads to better commercialization. In Japan, before 2004, all inventions in national universities were owned by the professor because the university was legally unable to own the IP. Despite its size, we were only able to identify two drugs that originated from Japanese PSRIs. In Canada, rules on IP ownership by universities vary across Provinces. The US passed what is widely considered landmark legislation, the Bayh-Dole Act in 1980, which allows 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. This model empowered US PSRIs to develop the most advanced technology transfer system in the world.

The UK abolished BTG's monopoly on British academic inventions in 1988, but mainland Europe didn't start abolishing the Professors' Privilege until 1999 in Denmark, was the first country to abolish the privilege, followed by Germany, Austria, Belgium, Czech Republic, UK, France in between 2001 and 2007 (Kilger and Bartenbach, 2002; PVA - MV, 2003; Iversen et al., 2007). Today only in Sweden does the rights to academic inventions still reside with the professor. Opportunities may be lost through these years. European institutions are now establishing offices of technology transfer at a rapid rate, though funding for these activities is an issue.

Another important related factor could be the levels of public funding for academic biomedical research. The US government support for such research, primarily provided through the National Institutes of Health (NIH) which is the world's largest public enterprise supporting basic research. During the past 15 years, NIH funding increased from 10.4 billion in 1994 to 31.2 billion in 2009. There are strong indications that the US has seen a sharper growth in biomedical research investment in the last decade than has Europe or other countries. NIH has typically constituted a substantially higher percentage of the gross domestic product than

equivalent funding levels by other governments: over twice the percentages for Japan and major continental European countries. 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.

However, it is noteworthy that not-for profit PPPs established in the last decade have been productive and have made a great contribution to the developing countries. DNDi established in 2003, has already received approval for three marketed drugs. Besides that, DNDi has seven clinical/post-registration and four preclinical projects underway. Since MMV’s founding in 1999, it has developed the largest malaria drug R&D portfolio with more than 50 projects and has launched one product, Coartem, which is currently approved by FDA and over 20 African countries, with two other products Eurartesim and Pyramax are on the way of registration. Acting in the public interest, these PPPs bridges the existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners. These PPPs encourage the development of new safe and effective medical products for neglected diseases and in the process help to achieve a critical public health objective.

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