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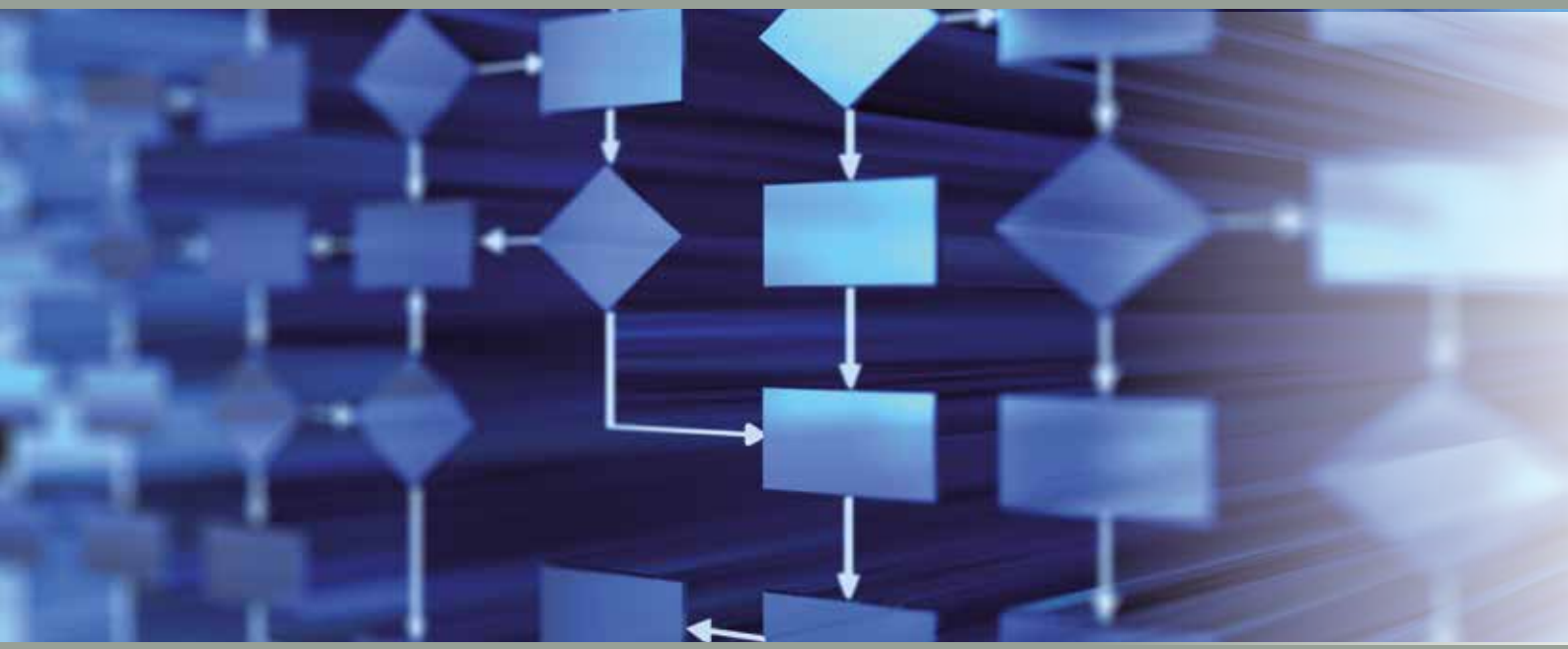

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# Sources of Biopharmaceutical Innovation: An Assessment of Intellectual Property

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**Abstract**

An analysis of FDA-approved new molecular entities reveals dynamism in terms of new innovation. An assessment of the first patent for each drug reveals that the pharmaceutical industry, particularly large, established companies in North America, tend to dominate the field. Over the past 10-15 years, European and Asian organizations have begun to close the gap. A dynamic inventive environment in drug discovery is suggested by the fact that NMEs for biologics or awarded to biotechnology companies often have inventors from the pharmaceutical and academic sectors. Whereas inventors continue to found biotechnology companies at a steady rate, recent trends suggest these inventors more often come from the private sector.

**Keywords**: *FDA, Patent, Intellectual Property, Firm founder*

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The views expressed in this article are those of the authors and do not necessarily reflect the views of the World Intellectual Property Organization or its member states.

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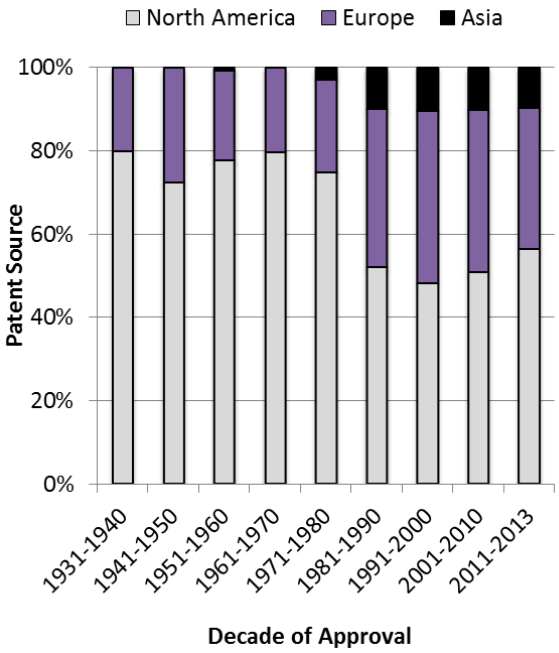
**Sources of Biopharmaceutical Innovation**

Invention has always been at the core of drug discovery. The sources of invention for FDA-approved drugs are constantly changing. Pharmaceutical companies, particularly those in North America, have generally been the most frequent source of first patents. However, increased diversity is reflected by the growth of ex-US sources of patents and increasing participation by biotechnology companies.

To assess sources of innovation in the creation of new medicines, we accumulated information about all new molecular entities (NMEs) approved by the United States Food and Drug Administration through the end of 2013 (Kinch et al, 2014). As one source of innovation, we identified the first-identifiable patent for each NME. This was performed primarily by analyzing databases from the US Patent and Trade Office (USPTO), the World Intellectual Property Organization (WIPO), SciFinder (American Chemical Society) and other public resources. Specifically, our approach sought to identify the earliest US patent approved for each NME based on its generic name. If this information was insufficient, secondary searches were performed based on the chemical structure and Chemical Abstracts Service (CAS) Registry numbers. Information was captured about the name, dates and locations of the inventors and the assignees. Importantly, the work herein focuses solely on the earliest application date to avoid variability in review times, which impact final decisions as to patent issuance. In cases, where the submission date occurred after FDA approval, these were presumed to reflect improvements (rather than the first patent) and were not included in this analysis.

This approach allowed us to determine the first identifiable patents for 1374 of 1453 NMEs approved by the FDA (95%). Importantly, the work herein focused on the earliest patent and did not consider additional intellectual property and/or trade secrets that may be crucial for making, marketing or gaining approval for a new medicine. While every attempt was made to identify the earliest patent, we cannot exclude that some patents for related molecules might have been filed prior to those associated with the specific identifier (generic name, chemical formula and/or CAS number).

***Figure 1: Geographic contribution to Patents***




*Notes: Source of first-identifiable patents for each FDA-approved NME*

***The location of the first inventor was broadly divided into North America, Europe, Asia and the Rest of World (ROW). The largest concentration of lead patent inventors was in North America, followed by Europe and Asia (***

Figure 1). When viewed over time, the geographic distribution of inventors of the first patents of FDA-approved NMEs has evolved. From the 1930s through the 1960s, approximately 80% of inventors and assignees were located in North America, with European contributors capturing most of the remaining patents.

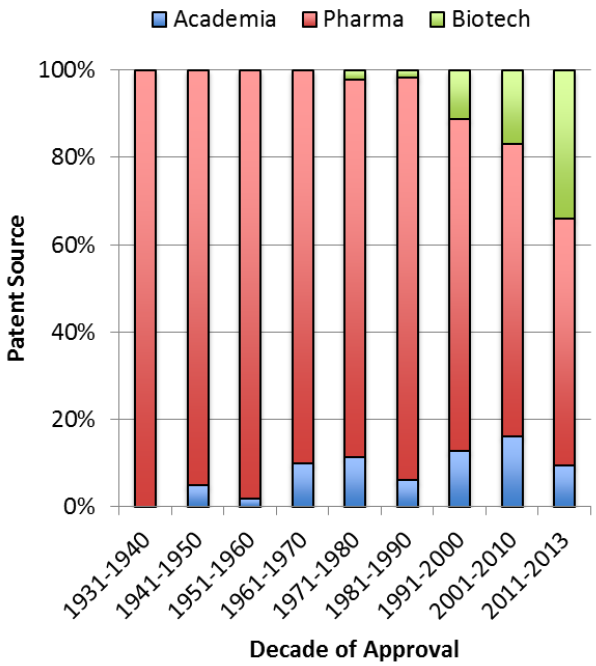
***Table 1: Five leading national sources (1931-2013)***

| Country | Patents |
|---|---|
| United States | 801 (58.3%) |
| Germany | 118 (8.6%) |
| United Kingdom | 95 (6.9%) |
| Japan | 89 (6.5%) |
| Switzerland | 69 (5.0%) |

*Notes: Source of first-identifiable patents for each FDA-approved NME*

Starting with NMEs approved in the 1970s, the proportion of patents awarded to European countries increased to approximately one-third and patents from Asia rose to almost 10%. In terms of individual nations (Table 1), the US contributed the largest number of first identifiable patents (810 or 58.3%) followed by Germany (118 or 8.6%), the United Kingdom (95 of 6.9%), Japan (89 or 6.5%) and Switzerland (69 or 5.0%).

***Figure 2: Organizational Contribution to Patents***




*Notes: Source of first-identifiable patents for each FDA-approved NME.*
*A total of 1374 patents were analyzed manually*

***Table 2: Five leading organizational sources (1931-2013)***

| Organization | Patents |
|---|---|
| Merck | 65 (4.7%) |
| Eli Lilly | 41 (3.3%) |
| Pfizer | 39 (2.8%) |
| Roche | 38 (2.8%) |
| Upjohn | 38 (2.8%) |

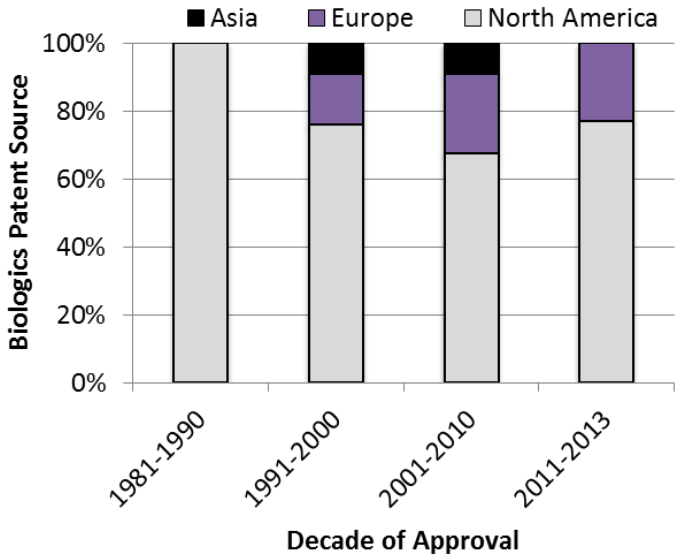
*Notes: Source of first-identifiable patents for each FDA-approved NME.*
*A total of 1374 patents were analyzed manually*

An analysis of patent assignees reveals a predominance of the pharmaceutical industry that persisted until recent years (Figure 2). Pharmaceutical companies were assigned the first patents for most NMEs (1118 or 81.4%) followed by academia (139 or 10.1%) and the biotechnology industry (8.5%). When assessing individual organizations, the most common assignees for the first identifiable patents were Merck (4.7%), Eli Lilly (3.3%), Pfizer (2.8%), Roche (2.8%) and Upjohn (2.8%), which together account for one six of all patents evaluated (Table 2).

## "Biotechnology" Patents

The rise of biotechnology began in the early 1970s and re-defined the discovery of new medicines (Evens and Kaitin, 2014; Russo, 2003). As one means of assessing biotechnology patents, we first limited our analysis to patents awarded for biologics-based products (generally polypeptide or antibody-based medicines). This necessarily limited the timeframe under investigation since the first biologic medicine was approved in the early 1980s. When analyzing geographic trends, comparable findings were obtained with biologics as has been seen with overall NME awards in that same time period. North American organizations were awarded approximately two-thirds of first identifiable patents for biologics-based medicines, followed by European and Asian organizations (Figure 3).

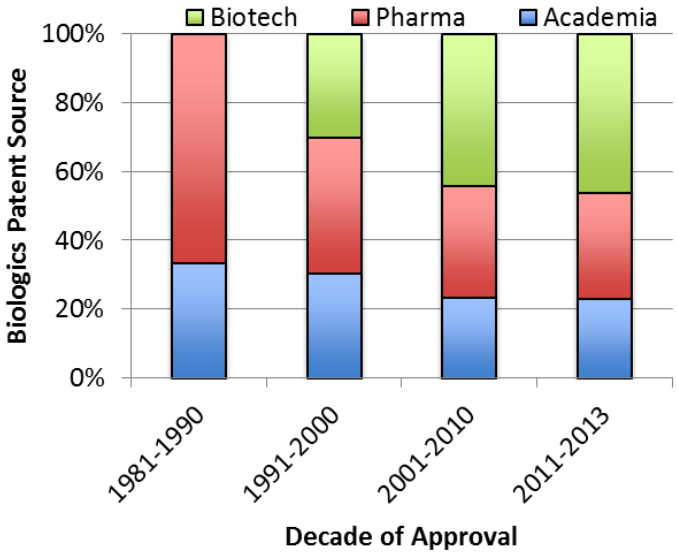
***Figure 3: Geographic Contribution to Biologics***




*Notes: Source of first-identifiable patents for each FDA-approved biologics NME.*

Academic organizations captured a larger proportion of biologics-based medicines than was observed in the assessment of all NMEs (Figure 4). Academic institutions (including government laboratories) were the source of inventors for the first patent for approximately one-quarter of all biologics-based medicines. Biotechnology and pharmaceutical companies share roughly the same number of NME first patents. Though, when viewed over time, biotechnology companies have increasingly displaced pharmaceutical companies.

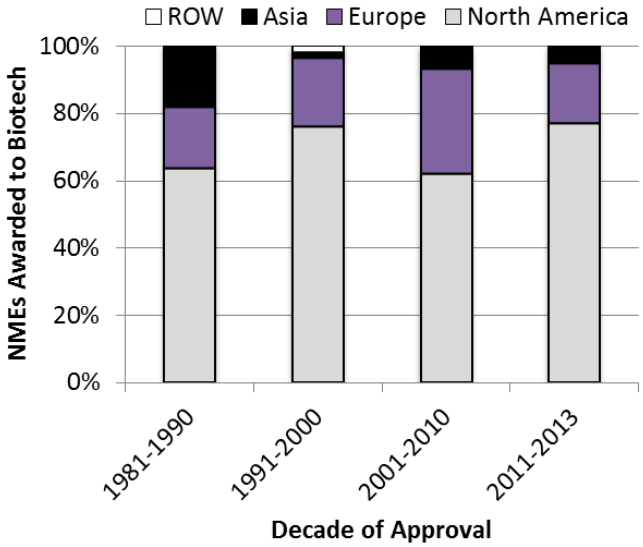
***Figure 4: Organizational Contribution to Biologics***




*Notes: Source of first-identifiable patents for each FDA-approved biologics NME. A total of 1374 patents were analyzed manually*

As we have emphasized in previous studies (see Kinch, 2014), a second way to define "biotechnology" is to analyze companies that were founded in or after the 1970s. A startup-based definition is imperfect but allows one to distinguish more conventional pharmaceutical companies (often founded in or before the 19th century) from more recent startups. When viewed in this way, the first approvals for biotechnology companies were obtained in the early 1980s and continue today. In total, 191 patents for NMEs were captured by this definition of "biotechnology."

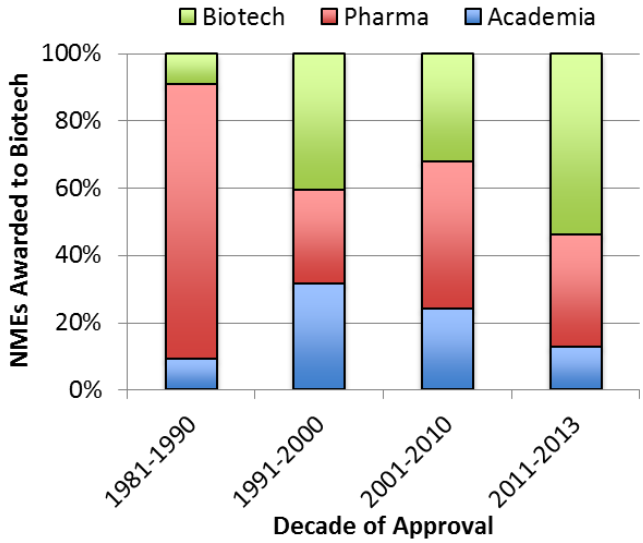
***Figure 5: Geographic Contribution to Biotech assigned NMEs***




*Notes: Source of first-identifiable patents for each FDA-approved NME assigned to biotechnology companies (founded on or after 1971) are indicated.*

The results for the more broad definition of biotechnology largely reflected that seen with biologics (Figure 6). North America contributed almost two-thirds of first patents, followed by European and Asian inventors. The leading countries in terms of hosting inventors of the first identifiable biotechnology patents were the United States with almost two-thirds (126 or 66.0%) followed by Germany (11 or 5.8%), Japan (10 or 5.2%), France (9 or 4.7%) and the United Kingdom (7 or 3.7%).

***Figure 6: Organizational Contribution to Biotech assigned NMEs***




*Notes: Source of first-identifiable patents for each FDA-approved NME assigned to biotechnology companies (founded on or after 1971) are indicated.*

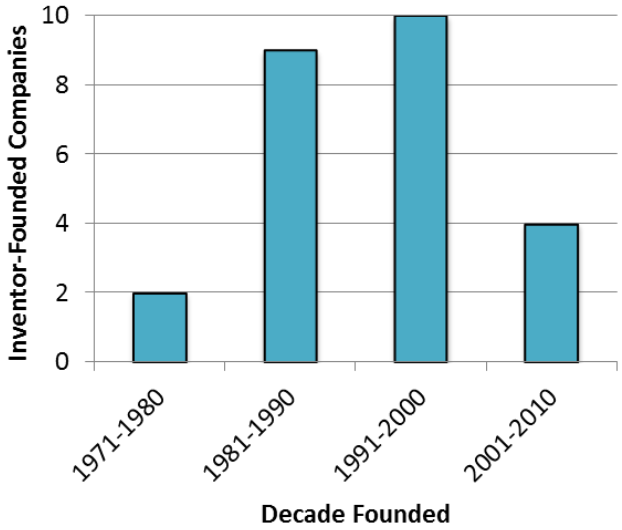
The first identifiable patents assignees for those NMEs ultimately awarded to “biotechnology” companies differed from those seen with overall NMEs. Pharmaceutical companies continued as a major source (Figure 6) representing today one third of all approved NMEs analyzed.

Academic assignees were more commonly linked with first identifiable patents awarded to biotechnology companies than had been seen with approvals awarded to pharmaceutical companies. The leading companies assigned the first identifiable biotechnology patents were Eli Lilly and Genentech (6 or 3.1% each) and Amgen (4 or 2.1%). Bayer, Biogen, and Rhone-Poulenc were each assignees for three (1.6%) of the first identifiable patents for biotechnology products. Two non-profit organizations, Sloan-Kettering Cancer Center and SRI International (3 or 1.6% each), were also amongst the leading institutions in terms of assignees.

## Patent inventors as founders

The founding of a biotechnology company represents another source of innovation for new medicine discovery. Many companies start up based on a promising new lead molecule or technology. Thus, we assessed the number of biotechnology companies where the inventor of the first patent was also a founder. These analyses were necessarily restricted to more recent approvals (from the mid-1960s through present day) due to limited availability of such information prior to that date.

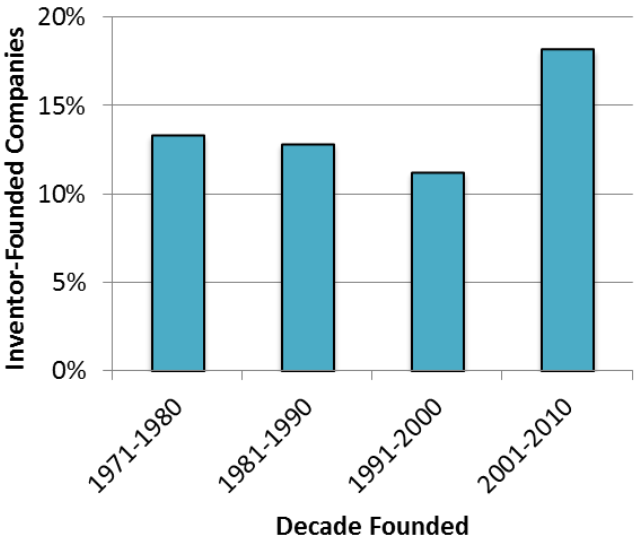
***Figure 7: Inventors as Biotechnology Company Founders (amount)***




*Notes: Biotech companies founded by an inventor of the first identifiable patent that ultimately led to an FDA-approved NME.*

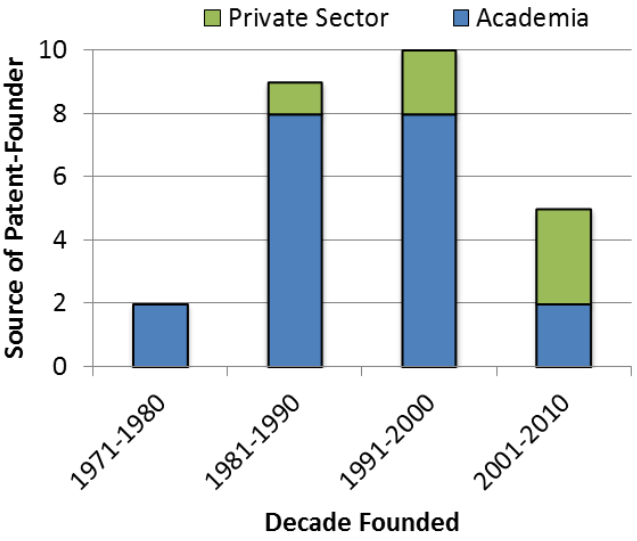
Overall, a founder was an inventor on the first patent for 26 companies that contributed to at least one NME approval. When viewed over time, the absolute number of companies where an inventor founded a company to advance the invention peaked in the 1980s and 1990s and declined somewhat thereafter (Figure 7). However, when viewed as a proportion of all biotechnology companies that have contributed to an NME approval (Figure 8), this trend is negated and the relative proportion remains steady.

***Figure 8: Inventors as Biotechnology Company Founders (share)***




*Notes: Biotech companies founded by an inventor of the first identifiable patent that ultimately led to an FDA-approved NME.*

***Figure 9: Original sector of Biotech Inventors-Founders***

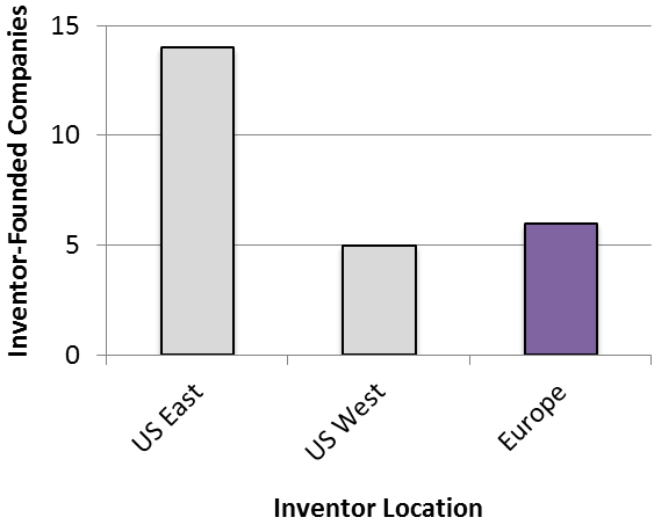



*Notes: Organizations employing inventor-founders previous company foundation.*

To assess further the link between patent inventors and founders, we evaluated the sources of these dual inventor-founders. This was defined by determining the organization in which the

founder was employed immediately prior to the foundation event. Of the companies founded by an inventor on the first patent, the inventor was most often employed by a university or government laboratory (77% of cases, see Figure 9). The remaining inventor-founders were employed in the private sector (primarily other biotechnology companies) immediately prior to the foundation event. The relative proportion of inventor-founders from the private sectors has increased in recent years. From a geographic standpoint, most inventor-founders (56%) were located in the eastern half of the United States, with the remaining almost equally divided between the western half of the US and Europe (Figure 10).

***Figure 10: Geographical distribution of Biotech Inventors-Founders***




*Notes: Organizations employing inventor-founders previous company foundation.*

## Outcomes and Implications

A major finding of our present study is that diversity of innovation for new medicines appears to be broadening, both in terms of geographic distribution and participation by academic, pharmaceutical and biotechnology organizations. While the early years of drug development were dominated by a relatively small number of North American companies, the past 30 years has witnessed increasing participation by European and Asian pharmaceutical companies. We cannot exclude that the early dominance of North American companies reflected, in part, the fact that the work herein focused on NMEs approved for use in the United States, which may therefore reflect a selection bias. The more recent increase in European and Asian companies may also reflect the fact many organizations have become more global over the past few decades, particularly in terms of intellectual property.

Pharmaceutical companies generally are still a major source of the first identifiable patents for approvals that are ultimately awarded to biotechnology companies. A general perception has been that biotechnology companies emphasize early-stage research whereas pharmaceutical companies become more involved in later-stage development activities. The work herein suggests this view is over-simplified since pharmaceutical companies continue to be major contributors of intellectual property for both biologics-based medicines in general as well as NMEs ultimately awarded to biotechnology companies. In the context of evidence that biotechnologies companies likewise often contribute to the discovery, research and

development of approvals awarded to pharmaceutical companies (Kinch, 2014), this suggests continued and bi-directional interactions among companies from both sectors. Indeed, the distinction between pharmaceutical and biotechnology companies (as defined herein) is increasingly blurred and has increasingly supported the accuracy of "biopharmaceuticals" as a more accurate descriptor.

While there are many articles evaluating the patent estates around particular targets or therapeutic applications, there are relatively few reviews of the larger question of overall patents. One of the few articles utilized patents in part to assess the current health of drug discovery (Kesselheim et al, 2013), as well as the impact of market exclusivity on innovation (Glover, 2007). Further interest in this field could itself be innovative and provide important advantages, in part, because patents can also be utilized to map technologies within the biopharmaceutical sector (Russo et al, 2013) and guide pricing strategies (Danzon and Towse, 2003). Furthermore, there is growing interest in key areas such as the potential use of intellectual property to regulate biosimilars (Zelenetz et al, 2011; Tsiftsoglou et al, 2013) and the proliferation of "me-too drugs" (Pekarsky, 2010)

Another interesting finding centers on the changing sources of innovation in terms of inventors, who also serve as company founders. The proportion of biotechnology companies founded by an inventor on the first patent has remained stable. Whereas the public sector (primarily academia) tended to be the major source of inventor-founders, the private sector has gained more prominence, particularly over the past 10-15 years. It is unclear at this time whether this is a durable trend. Nonetheless, such a finding may suggest increasing "professionalization" of corporate founders driven perhaps by investors, who tend to favor founders with past experience in drug development as a means of "de-risking" or increasing the probability of success.

Our studies herein provide a snapshot of two sources of innovation: inventors and start-up companies founded based on their inventions. Clearly, there are many other sources of innovation that are not captured by a simple analysis of the first awarded patent (Hine and Kapeleris, 2006). These range from basic scientific concepts through breakthrough technologies that facilitate the development and delivery of new medicines. Though, beyond the scope of our present report, it will be interesting to assess additional sources of biotechnology innovation arising from the myriad activities required for the research and development of new medicines.

***Acknowledgements***

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