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# Innovator Organizations in New Drug Development: Assessing the Sustainability of the Biopharmaceutical Industry

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The way new medicines are discovered and brought to market has fundamentally changed over the last 30 years. Our previous analysis showed that biotechnology companies had contributed significantly to the US Food and Drug Administration approval of new molecular entities up to the mid-1980s, when the trends started to decline. Although intriguing, the focus on biotechnology necessarily precluded the wider question of how the biopharmaceutical industry has been delivering on its goals to develop new drugs. Here, we present a comprehensive analysis of all biopharmaceutical innovators and uncover unexpected findings. The present biopharmaceutical industry grew steadily from 1800 to 1950 and then stagnated for two decades, before a burst of growth attributable to the biotechnology revolution took place; but consolidation has reduced the number of active and independent innovators to a level not experienced since 1945. The trajectories and trends we observe raise fundamental questions about biopharmaceutical innovators and the sustainability of the drug-development enterprise.

## Introduction

The biopharmaceutical enterprise has contributed fundamental improvements to the health and wealth of the developed world. According to PhRMA, the pharmaceutical industry sector is the most research and development (R&D)-intensive in the world (PhRMA, 2015), and makes an annual economic contribution of $790 billion, including employment of more than 800,000 workers in the United States alone. More importantly, the output of the pharmaceutical industry has had a remarkable impact on public health, as we now live longer and, overall, healthier lives from infancy to old age. Therefore, the sustainability of pharmaceutical enterprise is of significant importance both in terms of public health and economic viability.

It is widely understood that the biopharmaceutical industry is rather unique in terms of the transient nature of its products. Patent-protected products are tightly regulated and provide the mainstay of revenues (Caves et al., 1991). However, even the most efficacious and popular products will ultimately succumb to generic competition. This constant churn requires a robust pipeline of products to ensure continuity, thus explaining the need for high R&D expenditures. A recent report suggests that the average costs of developing a new drug now exceed $2 billion (Mullard, 2014). Such eye-wateringly large numbers reflect the increasing costs of clinical investigation and declining efficiency. According to insightful and entertaining discussions by Munos (2009) and Scannell et al. (2012), the declining productivity in new product development can be measured using a logarithmic scale and gives rise to a trend they termed ''Eroom's Law,'' a playful inversion of Moore's Law of computer processing power. To counter the consequences of Eroom's Law, the biopharmaceutical industry has experimented with ways to maximize the reward while minimizing the risks associated with drug discovery and development. Unfortunately, these measures include decreased participation by many established companies in the early stages of R&D (Kola and Landis, 2004). We have been interested in analyzing the sources of pharmaceutical innovation for a number of years now as a way of getting a deeper insight into what drives innovation in this area, how we can assess the health and robustness of the industry, and to make recommendations for ensuring the long-term growth and viability of the biopharmaceutical enterprise, not only for its own benefit, but, more importantly, for the benefit of global public health.

The project began as an attempt to catalog all new molecular entities (NMEs) ever approved by the US Food and Drug Administration (FDA) (Kinch et al., 2014a). In doing so, we identified the organizations that had contributed to the research or development of new medicines, ranging from the submission of the investigational new drug (IND) application through to the final approval by the FDA (Kinch, 2014). These companies will hereafter be referred to as ''innovator'' or ''successful'' companies. Based on many high visibility mergers and acquisitions, we also tracked the fate of those organizations, which revealed patterns of consolidation over time that largely erased the gains in innovator biotechnology organizations (those founded after 1970) to a level not seen since the mid-1980s (Kinch, 2016).

Our previous analysis used an imperfect definition of ''biotechnology'' based on the year each company was formed, and defined biotechnology companies as those formed in or after 1971. This left out the contributions and fate of the remaining ''pharmaceutical'' companies that were founded before 1971. Here, we address this gap by taking a broader and more detailed look at the fate of all companies involved in the business of developing new medicines, referred to here as ''biopharmaceutical'' companies. Our analysis identified 312 innovator biopharmaceutical companies that had produced FDA-approved

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medicines, from the beginning of FDA record keeping through to the end of 2015. The participants range from Merck, founded in 1668, to companies established just a few years prior to product approval. The dynamics of where and when these innovator companies were formed, as well as their fate over time, reveals waves of foundation and consolidation. Looking beyond this pattern, the overall trend is troubling as we see that the number of innovator organizations actively participating in new medicine development has plummeted to a level not witnessed since the Second World War, raising important questions about the sustainability of new drug development.

## Data Gathering Phase

To identify the sources for all FDA-approved medicines, we initiated an extensive analysis of the organizations participating in their research or development by reviewing documentation publically available on the FDA website. Specifically, the medical and pharmacology reviews of each new molecular entity (NME or active ingredient) were analyzed to identify both the "successful" organization submitting the approval as well as all organizations participating in the development of the drug as reported to the FDA. Extensive FDA documentation was not available for many medicines approved before the mid-1990s. We addressed this deficiency by conducting additional research of the scientific, medical, and commercial literature detailing the drug products and the companies sponsoring the R&D activities. Particular emphasis was placed on publically available databases, including those from the National Library of Medicine of the NIH and the US Patent and Trademark Office; the latter was used to identify both patents and trademarks. We pulled from all these resources to create a database that includes both the approved medicine and the organizations that contributed to the preclinical and clinical activities ranging from the submission of the IND through to the final licensure by the FDA. This aggregated list of organizations was the starting point for the next layer of analysis as we set out to determine the foundation and fate of each company by searching numerous resources including company websites and press releases, with emphasis on identifying key dates and locations of all relevant organizations. At the end, our analysis revealed that 311 different companies have contributed to the research or development of an FDA-approved NME.

## Growth of the Pharmaceutical Industry

The earliest foundation event we could identify was the 1668 creation of the Merck company, which was split to Merck & Co. and Merck KGaA as a result of American confiscation of German-owned properties during the First World War. Merck was established in the city of Darmstadt in the Landgraviate of Hesse (now Germany) and later went on to discover and market morphine, the widespread use of which, starting in 1827, predated the formation of the modern FDA by more than a century (Vagelos and Galambos, 2004). In the early days of the biopharmaceutical industry, the formation of these companies, which would later go on to generate an FDA-approved medicine, occurred at a low and somewhat sporadic rate of fewer than one new entrant per year until 1880 (Figure 1A). Thereafter, the number of new entries generally exceeded one per year until the middle of the 20th century. At that point, the net number of biopharmaceutical companies contributing to FDA-approved drugs barely exceeded 100 (Figure 1B). Over the following two decades (from 1951 to 1970), formation of new innovator biopharmaceutical companies stalled again, with the rate dropping below one new entrant per year.

Looking at the geographic distribution of pharmaceutical innovator companies founded during the 1668 to 1970 period, most of them were located in North America (N = 52) and Europe (N = 48), with fewer (N = 19) in Australasia, a large area encompassing Asia and Australia and Oceania, and none in Africa, or Central and South America (Figure 1C). Closer inspection of the location data indicates that, during this time period, conventional pharmaceutical companies were widely dispersed throughout North America and Europe, and, although they tended to be found in or near major financial centers or places with the largest populations (e.g., London, Paris, New York, Tokyo, etc.), no standout preferred geographic areas emerged.

The "biotechnology" revolution began in the 1970s and can be seen as a dramatic spike in the formation of new companies (Kinch, 2014). Unlike the previous era, the biotechnology era was largely restricted to North America and parts of Europe (Figure 1C). Whereas the rate of company foundation was limited to an average of roughly one per year in Europe from the period spanning 1971 to 2000, North American company formation was 6-fold higher. A more detailed analysis of North American innovators reveals an interesting trend (Figure 1D). Historically, "successful" companies founded over a period of more than a century and a half, stretching from 1800 to 1970, were equally located in either the Northeastern or Midwestern United States. In contrast, the growth associated with the US biotechnology revolution happened primarily in the Northeast and the West Coast. Although some additional growth was observed in the Midwest United States, Southeast United States, and Canada, these areas are less-well represented than might have been expected based on the larger trends over time.

## Stagnation then Consolidation

Our analysis of company creation revealed a steady accumulation of experienced companies that continued largely uninterrupted from the beginnings of the 19th century until the early 1950s (Figure 1A). Relatively few of these companies were either subject to consolidation or underwent bankruptcy. From 1801 to 1952, we recorded only three exits: Davis & Geck and Lederle Laboratories were purchased by American Cyanamid in 1930, and Bayer was merged into IG Farben in 1925. As a consequence of steady growth and infrequent exits, the net number of active and independent organizations participating in pharmaceutical R&D that had success in obtaining FDA approval and delivering NMEs to market exceeded 100 by 1950 (Figure 1C). The two decades thereafter saw stagnation in the number of innovators as new entries were entirely offset by corporate acquisitions.

As documented elsewhere, the biotechnology explosion in the latter quarter of the 20th century witnessed an impressive increase in the net number of successful organizations that had contributed to the research or development of an FDA-approved medicine. However, undermining this increase in the number of new companies entering the arena was a gradual exit of many companies as first the pharmaceutical, and later biotechnology, sectors went through a period of industry consolidation