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PERSPECTIVE

WANTED DEAD OR ALIVE: New Thinking to Incentivize Drug Development

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Abstract
Despite unprecedented advancements in our understanding of disease process and targeting opportunities, our continued ability to discover and develop new medicines is fundamentally in doubt. These challenges reflect a growing recognition of the escalating risks of drug development (in terms of dollars and time) by established pharmaceutical companies and investors. Such hurdles are surmountable and require new thinking. This opinion piece conveys an overview of the challenge and an example of how we might overcome these challenges with constructive and forward-looking incentives for drug discovery.

Keywords discovery · drug development · Eroom's law · innovation

Introduction

Our ability to develop future medicines is increasingly a subject of considerable concern. This notion might seem absurd given that our knowledge of health and disease continues to grow exponentially. Yet an inability to understand causes of disease are not the limitations that threaten drug development. Rather, the challenge is our ability to span the divide between fundamental knowledge and its application. Medicines are amongst the most highly regulated products with development costs measured in billions of dollars and more than a decade of hard work [1, 2]. Moreover, our efficiency in developing new medicines has been declining persistently for at least 75 years [3].

This problem is well known and has acquired several monikers, including the "Valley of Death" and the "Great Divide." Arguably the best descriptor is Eroom's Law, a playful inversion of the Moore's law of computing [4]. This designation contrasts the consistent improvements in the efficiency of computer processing speed, as popularized by Gilbert Moore (of Moore's Law fame). The inversion of the surname reflect the fact that whereas the efficiency of computing speed has consistently improved over time, the efficiency of drug discovery has persistently declined [5]. Indeed, the research that triggered the naming of Eroom's Law revealed that the cost to develop a new medicine has been increasing at an exponential rate since at least the 1950s [3].

Analyses of the sources of pharmaceutical innovation suggest that the pharmaceutical industry began reacting to Eroom's law in the mid-1970s. These concerns compelled many attempts to circumvent the law, all of which have proven ineffective or counterproductive. The attempts include emphasis upon me-too drugs (fast followers), embracing high-margin niche markets (e.g., orphan indications and oncology) and avoiding perceived low margin or demand products, (e.g., antibiotics) (Fig. 1).

The example of antibiotics is particularly relevant given that market forces diminished the value of antibiotics just as microbial resistance became commonplace. The experience of the drug vancomycin reveals the challenge. Vancomycin was sufficiently innovative that the drug was literally and figuratively put on a shelf to limit its overuse. This was a highly rational public health decision given the abuses of antibiotics, which have compromised their long-term usefulness. Consequently, the organization that developed vancomycin would not realize its value. By the time that the product would indeed become more widely deployed, its patent protection had expired, and the profits were realized by generic manufacturers, not by the originator. Unsurprisingly, the originator abandoned further antibiotic research, a decision that was mimicked by other companies in the years following. As such, the saga of vancomycin provided a valuable lesson taught in many a corporate board room for years to come.

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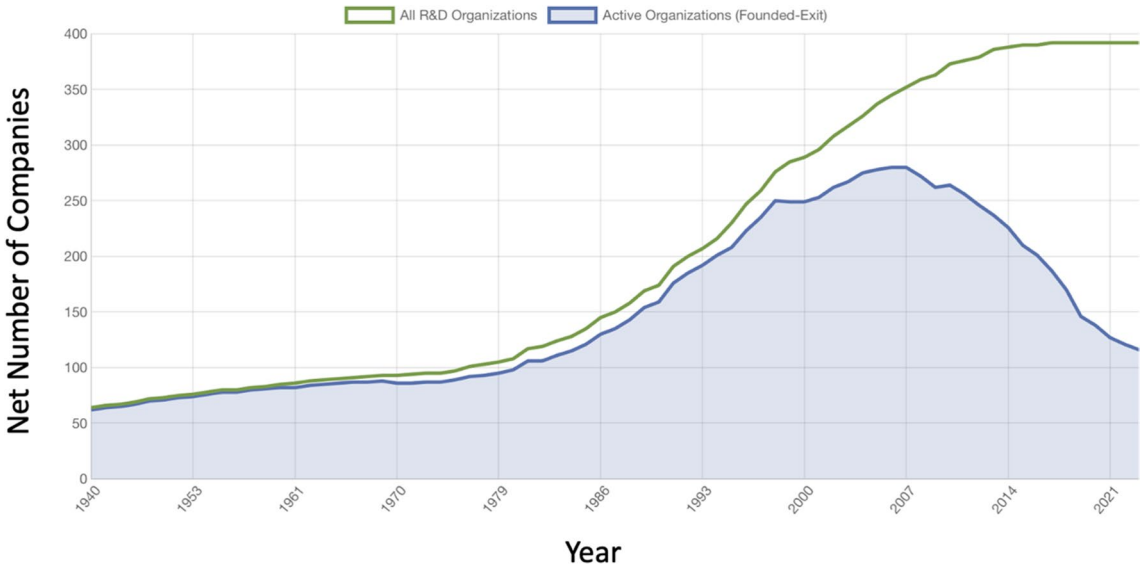

Fig. 1 Shown is the number of companies that have previously obtained an FDA approval and that are still active in new pharmaceutical research and development. The information was aggregated and analyzed using the Clincal Drug Experience Knowledgebase (CDEK, cdek.liu.edu).

Beyond creating discordance between market and public health needs, another response to Eroom's Law was an emphasis upon industry consolidation [6]. Objective and measurable evidence reveals that pharmaceutical development has become ever more reliant upon mergers, acquisitions, and licensing. In the earliest stages of this approach, much of the deal making centered either on companies with either approved or late-stage drug development programs. This strategy eliminated much of the risks that were associated with early-stage products. Over the past half century, the efficiency and convenience of such acquisitions has evolved into a dependence. Presently, comparatively few "big pharma" companies have robust discovery or early development efforts. Most of those remaining are mere shadows of past efforts.

At first glance, the interdependence between companies, large and small, established and start-up, early and late-stage development, does not itself seem to pose a particular cause for concern. After all, the logic goes, an acquired company is simply subsumed into the acquirer. Looking more closely, the problems come into focus.

The announcement of mergers is inevitably followed shortly thereafter by waves of layoffs and downsizing of both the acquired employees as well as staff from the acquirer (often to offset resources that were committed to the acquisition) [7]. Another concern is that an acquisition generally involves a company that has successfully and efficiently developed one or more promising products. During the transition or amidst layoffs that almost invariably follow mergers, such efficiencies are frequently lost as teams are disbanded or disrupted. Even were a laid off team to reform into a new venture, the activities needed for this new start-up to acquire funding would invariably negatively impact overall productivity. Such outcomes thus ensure continued adherence to Eroom's Law, which in part explains the persistence of this negative trend for more than seven decades.

Another view of this phenomenon is to consider the modern pharmaceutical industry as being akin to a terrestrial ecosystem. Such networks range from top predators to other hunters, large and small, down to herbivores and the plants that they require for sustenance. The problem, our data suggest, likely lies at the bottom, which is often invisible from the highest peaks of the food chain [6].

A simple glance at the rates of corporate formation and dissolution suggests that the number of start-ups that are committed to the development of new pharmaceutical products is not keeping pace with the rate of corporate acquisitions [8]. As one pharmaceutical executive has told me, "Our company, and all of our peers, are aware of every phase 3 and phase 2 clinical-stage asset. These are highly picked over. We increasingly find ourselves having to consider phase 1 and even preclinical assets." Stated another way, we are eating and not replacing more and more of the proverbial seed corn. Such activities rely upon faith and presumptions that future harvests will spontaneously arise.

The pharmaceutical industry has managed to get by with such a strategy. The number of startups arising from academic laboratories has been robust; sufficient to satiate the needs of a fast growing food chain in a mature industry [9]. However, the portents of a problem are easy to spot. For one thing, investors seeking a high multiple on their investment are increasingly cognizant of Eroom's Law. This awareness of declining efficiency likely raised questions about committing fortunes to endeavors that might require a decade of

clinical-stage investigation to yield a payoff. A combination of high risks with impatience, they might reason, does not seem as daunting for other technologies that are less tightly regulated, have lower barriers to entry, and are quicker to generate profitability. Compounding the concern, the past decade and its historically low interest rates had incentivized many investors to consider higher-risk endeavors to gain a higher return. This era appears to be nearing an end, to be replaced by an extended period of higher interest rates. Consequently, other financial vehicles might become more attractive than higher-risk biotech start-ups.

The urgency of this growing problem is particularly challenging for some commonsensical reasons. First, the decade-long lag that separates early development from product approval means that a slowdown in the global portfolio of promising new medicines may go unnoticed for years.

Rather than simply awaiting a disruption in the discovery or development of new therapeutics, it is important now to consider both the fundamental problems that have decreased the attractiveness of drug development, as well as ways to incentivize these crucial activities. For this, we return to the example of antibiotics.

One possible solution may arise from innovative approaches that originated in the world of criminal justice. In 2010, British Justice Secretary Jack Straw announced the creation of a "social impact bond" to finance a prisoner rehabilitation program [10]. This financial vehicle defines a problem to be solved and attaches a success fee to innovators that achieve the goal. The concept is analogous to an Old West bounty akin to "Wanted: Dead or Alive."

The key to this approach is that the bounty must be set at a level that is perceived to provide value to those, both who post and receive the reward. When this level is understood, a social impact bond can attract enough bounty hunters, investor-backed entrepreneurs, to address the challenge. If we substitute a new and improved antibiotic for a Wild West desperado, then we can begin to appreciate how and why this approach might prove useful.

Indeed, the idea of a bounty has already been introduced into the sciences. One example is the InnoCentive challenges from the Wazoku, a London-based software company. This organization sponsors competitions for inventive ideas, awarding thousands of dollars for successful concepts. Were such a model to be amplified manifold, it could be utilized to provide multi-million or billion dollar incentives for much-needed public health measures, such as antibiotics.

Investor perceptions that antibiotic development is insufficiently valuable could be offset by social impact bonds that encourage greater risk taking and higher payoffs. Were we to rewind history and apply this model to vancomycin, its innovator might have been sufficiently rewarded to remain in the hunt for newer and even better antibiotics. A more contemporary example may be the situation with COVID-19 vaccines. In the early days of the pandemic, the world craved a vaccine and much investment, private and public, was invested into these lifesaving preventatives. However, a rather dramatic decline in vaccine uptake and booster shots has translated into massive negative implications for vaccine manufacturers; with one example being that this shortfall was cited as the primary reason for Pfizer's decision to furlough roughly one-quarter of its staff in 2023 [11]. Beyond the immediate impact on Pfizer and other manufacturers, these actions could have dire implications for the future of new vaccine discovery and development. A social impact bond could provide an opportunity to incentivize future public health endeavors.

Nor would a social impact bond model be limited to governmental organizations. A similar mechanism might be comparably applicable to the goals of certain non-profits (e.g., Gates Foundation, Chan Zuckerberg Initiative, etc.) and patient advocates, who might contribute to the bounties for diseases of interest.

While we do not expect a social impact bond strategy to provide a panacea for all public health issues, the innovation needed to develop new generations of medicines may not be limited to the pharmaceutical industry. Considerable value might be gained by leveraging new ideas in both the science and incentivization schemas to realize future biomedical breakthroughs.

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Data availability All data can be accessed at cdek.liu.edu.

Declarations

Conflicts of Interests/Competing Interests The author has no conflicting or competing interests with the subject matter cited herein.

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