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Viewpoint

The New Paradigm in Pharma R&D

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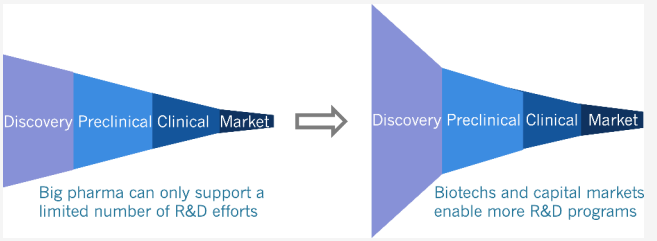
ABSTRACT: Drug discovery has seen dramatic change over the last 25 years. The vertically integrated large company model prevalent for more than 50 years has at least partly been replaced with a more distributed drug discovery enterprise that includes large numbers of small research organizations.



KEYWORDS: *pharma industry productivity, new drug discovery paradigm, small biotechs*

The environment for drug discovery has undergone a major transformation over the last approximately 25 years. This change was brought about by a variety of market and scientific forces. In general, it has led the industry away from the culture that existed from the 1950s until around 2000[1] that consisted of a small number of large vertically integrated drug companies to a more heterogeneous global discovery enterprise that includes a wide variety of small companies, contract research organizations (CRO), and academic laboratories.

There was a period in the early 2000s where one of the hottest topics in the industry was the crisis brewing in pharma. There was a growing concern that the pace of drug discovery was slowing even as costs were escalating rapidly. In addition, the increasingly gloomy atmosphere was driven by legitimate fear in the community about job losses[2] and the growing trend of outsourcing many research capabilities to small CROs, particularly in Asia. The concerns were real with the industry facing significant job losses for the first time in decades.

"Doomsday graphs" began appearing at meetings and in the literature that showed a steep and worrying downward trend in research productivity from 1950 to 2010.[3] Similarly, a perceived reduction in the number of drugs being approved[4] during the early part of the 2000s (Figure 1) was offered as further evidence that something had fundamentally changed in the industry. If one ignores the approvals after 2010 (green box) and focuses on the approvals beginning in 1996 (red box), one might perceive a downward trend.

These were unsettling times driven by growing concerns that the whole industry might be reaching a point where the pace of drug discovery was irrevocably in decline. While it is impossible to dismiss the dislocations in the industry and corresponding trauma that ensued, I would argue that in many ways the industry would eventually develop an alternative landscape that is more productive rather than less (Table 1, Figure 1 green box).

In fits and starts, the industry has evolved from a model where a small number of vertically integrated drug companies, primarily in the US and Europe, were responsible for the discovery of almost all new drugs to a model where drug discovery is widely distributed across big and small entities (both commercial and academic) worldwide. The early part of the decade from 2000 to 2010 saw developments that would have previously been unthinkable. Compounds, and all manner of IP, were being shipped to and from a network of independent CROs around the world as big pharma began adopting strategies to outsource discovery functions and reduce costs.

As the decade progressed more discovery services companies sprang up[5] to take on ever more critical functions including synthesis, screening, pharmacokinetics, modeling, and structural biology. Cost was undoubtedly a driver of this trend, but in the end the changes were more profound. The number of small discovery-based biotechs and academic discovery efforts, particularly in the US, also began to grow. In some ways these new entrants were enabled by ready access to external research capabilities that previously had to be replicated internally, and the concept of virtual organizations[6] became more prominent.

The move to outsource large parts of the discovery enterprise at big pharma was, apart from cost, counterintuitive in many ways. Big pharma enjoyed enormous advantages with their resources, history of developing much of the specialized expertise required to discover drugs internally (almost as an apprentice system), and well-oiled infrastructure at every stage

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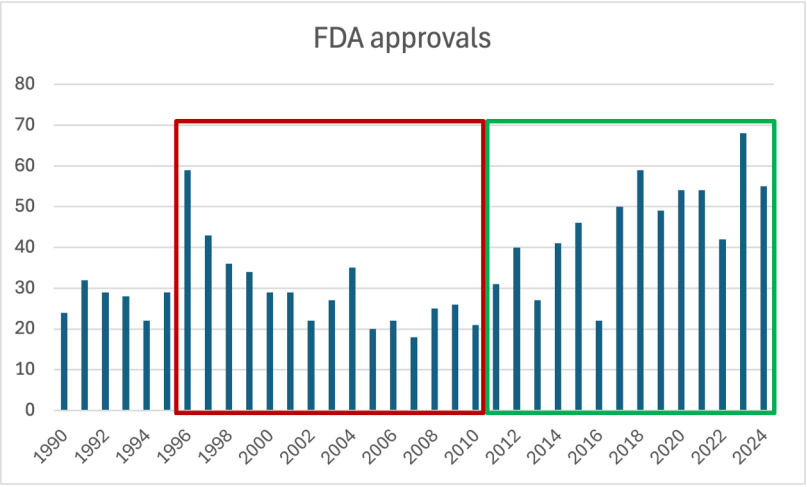

Figure 1. New FDA approvals 1990−2024.

Table 1. FDA Approvals from 1996 to 2024 in Five-Year Intervals

Years	Mean	Median
1996−2000	33	34
2001−2005	27	27
2006−2010	22	22
2011−2015	37	40
2016−2020	47	50
2021−2024	55	55

of bringing new drugs to market. Moreover, I think it is fair to say that the quality, experience, and capabilities at some of the new CROs was not initially comparable to the capabilities in big pharma. There was, of course, a learning curve, but over time the CROs caught up. Indeed, in some cases their expertise and capabilities arguably exceeded some big pharma capabilities, particularly as technology leaders in newer disciplines, including quite a few academics, began starting their own companies. Some areas where this trend was apparent were structural biology, modeling, biophysical screening, fragment-based design, and now AI/ML.

As it turns out there are some inherent advantages enjoyed by small companies. This might seem strange given big pharma has more resources, some of the most talented scientists in the world, and a global infrastructure no small company could hope to match. But small companies have, in my opinion, at least three structural advantages that no large drug company can replicate.

First, small companies have an enormous cost advantage. This is not because they do not compensate their employees competitively but is a consequence of the high overhead at large pharma companies. This can be illustrated by looking at CEO compensation in the industry. According to Fierce Pharma the top 10 industry CEOs collectively earned more than $235 million dollars in 2023.[7] This is just a small fraction of the real cost given the many levels of management present in large multinational drug companies. This enormous overhead must be absorbed in the fully loaded FTE cost at a Johnson & Johnson, Merck, Pfizer, or other traditional large drug company. Small research-based biotechs simply do not have as many executives, and their compensation is for the most part contingent on success. The fully loaded FTE cost at a small research-based biotech enjoys an advantage that is impossible for large companies to match.

The second advantage small companies have is focus. In my experience the traditional big drug companies have implemented ever more complex stage gate systems[8] aimed at making earlier decisions about the probable success of research programs. One often hears the term "fail early." The problem is that any decision to terminate a drug discovery program has, based on industry norms, an 80−90% chance of being correct, but all the value is in the cases where this decision would be incorrect. Moreover, anyone familiar with the industry knows that many, if not most, ultimately successful programs go through difficult periods where success looks far from certain. This is when they are most vulnerable to overzealous management. Indeed, the drug lore is replete with examples of successful programs that only made it because enterprising managers and/or scientists actively resisted efforts to kill the program. Some of these examples are described in entertaining drug discovery books by J. J. Li[9] and R. L. Shook.[10] Small research-based companies do not have the luxury of killing programs at the first sign of trouble. They generally only have one or a small number of programs in the first place. This makes small organizations more invested in the success of their program[s] and, I submit, engenders a certain doggedness that may be missing from larger organizations. I have witnessed this phenomenon many times from both sides.

The third key advantage small companies have is organizational alignment. In small discovery organizations it is much easier for everyone from the CEO to the bench to have a consistent understanding of the goals and stakes of their work. This is difficult in large organizations as highlighted by the oft-quoted management concept of the "Organizational Iceberg." This business concept, widely credited to S. Yoshido in spite of scant documentation, posits that information management in large organizations resembles an iceberg, where the vast majority of information and problems in an organization are not visible to senior management, i.e. under water.[11] In this analogy, 100% of problems are apparent to front-line employees, but the percentage drops with each layer of management until in many large organizations as little as 4% may be known to senior management. One might argue with the percentages, but I have personally seen the "iceberg" in action, particularly as regards the deep-seated reluctance in many, if not all, organizations to report bad news to senior management. By contrast, in most of the small research companies I have worked with over the last more

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than decade, senior management are too directly involved to ever be that far out of the loop.

Finally, I would assert that small research entities routinely assume greater risks than traditional big pharma, including the employees who work there. I once had a scientist in my organization express the gallows humor that in small biotechs "if you fail to bring a drug forward the company fails and you lose your job, but if you succeed the company disbands discovery to resource development and you still lose your job." I have unfortunately seen the second scenario play out more than once. It is just another risk big pharma can outsource in the current environment, and it creates a more dynamic, and risky, job market for scientists engaged in drug research.

The highly distributed drug discovery environment now operating (Figure 2) provides significant advantages to the

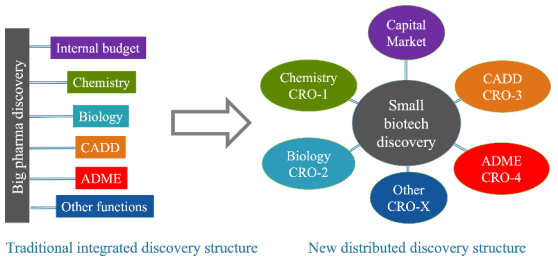

Figure 2. Integrated and distributed discovery models.

industry at large, but particularly to the traditional large pharma players. Some of these advantages include access to global equity markets to fund high risk early discovery programs and a major expansion of the front of the drug development funnel, as many more independent drug discovery programs go forward than could have been funded or managed internally by the traditional players. This has led major pharma companies to place an emphasis on identifying assets emerging from small biotechs with an eye to acquisition, i.e. "shopping" rather than "discovering."

The outsize impact of small companies is evident in recent FDA approvals.[12] Of the 55 drugs approved in 2024 (Table 1), only 23 were sponsored by companies with sales of at least $3 billion.[13] The small company contributions included some of the most innovative new approvals (Fierce Pharma).[14] The true impact is likely greater since some of the approvals from large pharma were probably in-licensed from a smaller company at some point.

The trend of relying increasingly on a broad collection of small companies and academic groups for early drug discovery has become deeply entrenched. However, there are storm clouds on the horizon. Raising capital has recently become more difficult due to a variety of economic factors, and unprecedented uncertainty has emerged around the role and funding capacity of critical government institutions like the NIH. Both developments threaten to make funding for small companies or academic to commercial transitions more difficult to obtain, at least in the US, and could significantly impact future R&D productivity.

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Notes

No unexpected or unusually high safety hazards were encountered.

The author declares no competing financial interest.

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ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AI	Artificial intelligence
CADD	Computer-aided drug design
CRO	Contract research organization
FDA	Food and Drug Administration
IP	Intellectual property
FTE	Full time employee
ML	Machine learning
R&D	Research and development
US	United States

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