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The R&D productivity challenge: transforming the pharmaceutical ecosystem

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The persistent decline in pharmaceutical R&D productivity has been extensively analyzed and debated for over two decades, with profound implications for the structure and strategy of the pharmaceutical industry. This systemic challenge forced many leading companies to adapt their R&D models, influencing internal capabilities and external innovation strategies. In response, the industry has evolved into a complex, interdependent biopharmaceutical ecosystem encompassing large pharmaceutical corporations, biotech innovators and specialized service providers. Although R&D productivity affects all research-driven companies, its consequences are particularly pronounced for large pharmaceutical firms, because the scale and capital intensity of their R&D activities make productivity a crucial determinant of long-term competitiveness and sustainability. By contrast, other stakeholders are only partially adversely affected, whereas some can even obtain value from it.

Keywords: Pharmaceutical industry; research and development; business model; blockbuster; drug discovery; R&D productivity; R&D efficiency

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Introduction: R&D productivity is a challenge for research-based pharmaceutical companies

Productivity of pharmaceutical R&D, understood as a return-on-R&D investment rate[(p1)] [i.e., how efficiently a R&D organization converts resources into defined outputs such as new drug launches (R&D efficiency)[(p2)] or how effectively it captures medical or commercial value from them (R&D effectiveness)[(p2)]] has been an extensively researched investigation for >20 years. This issue impacts the entire pharmaceutical industry, across different types of pharmaceutical and biotech companies.[(p1),(p2),(p3),(p4),(p5),(p6)]

Key factors contributing to low R&D productivity include:

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- High complexity of science and technology: multifactorial diseases, personalized medicine, advanced screening methods, new therapeutic modalities such as gene and cell therapies and the integration of data science and AI are all examples of an increasingly complex drug discovery landscape.
- High regulatory hurdles for drug development and new drug approval: heightened safety and efficacy standards, longer and more-complex clinical trial requirements and stricter post-market surveillance significantly impact the effort required for R&D.[p7],[p8],[p9]
- Long R&D timelines: drug discovery, preclinical and clinical development cycle times are becoming longer across the industry with an average timeline for drug discovery and development of 14 years.[p2]
- High drug discovery and development costs: with more-complex technologies, R&D expenses increase and accumulate over time, leading to the substantial cost per newly approved drug of >US $2.6B.[p10],[p11]
- Expensive technology and asset acquisition: leading pharma companies require significant investments in technology and external assets to manage the complexity of biomedical science and to fill R&D pipeline gaps, amounting to >US$500B between 2012 and 2021.[p12]
- Low (clinical) success rates: the probability of successfully developing a new drug from first-in-human to market is just 14.3%.[p13]

At the core of its definition is the steadily rising cost per new drug – a trend referred to as Eroom's Law.[p1],[p2],[p3],[p4],[p5],[p6] However, in recent years, the FDA has approved a record number of new drugs, raising hopes for improved R&D productivity and prompting some to argue that Eroom's Law might be breaking.[p1] From our perspective, the actual situation is likely to be different.

- Despite a significant rise in R&D investments by the industry, public institutions and venture capitalists, reaching US$271B in 2021,[p14] up from an estimated US$50B by leading companies in 2007,[p2] the number of new drug approvals has not increased at the same pace.[p15],[p16]
- The relative R&D output of leading pharmaceutical companies has declined, in terms of the number of new drugs and the quality of innovation.[p17]
- The increase in FDA drug approvals can largely be attributed to smaller companies focusing on niche indications, such as rare disease, particularly in the past decade (Figure 1).

As a result, the ever-increasing R&D costs per new drug have offset the industry's gains in approvals, indicating that overall R&D productivity has not improved.[p6] Beyond this open and debatable question of whether Eroom's Law still holds, many other aspects of the industry's R&D productivity crisis remain insufficiently understood and unresolved; for example, the question of which actors in biopharmaceutical ecosystems are more affected by this challenge. Building on this understanding, we asked whether R&D productivity represents a broad challenge for the entire pharmaceutical sector or is it primarily an issue for big pharma. To address this, (i) we discuss R&D productivity through the lens of business models and (ii) we approach it as a qualitative consideration rather than a quantitative analysis of R&D outcomes.

Big pharma's business model in context of R&D productivity

Big pharma companies traditionally constitute the oligopolistic core of the industry.[p18] For these leading companies, R&D productivity is a corporate challenge of such magnitude that it raises concerns about the long-term sustainability of their innovation-driven business models[p19] (i.e., how they create and capture value through R&D). For instance, between 2001 and 2020 nearly half of the leading pharmaceutical companies had to compensate for their negative R&D productivity through mergers and acquisitions (M&As).[p19] In response to this challenge, leading companies have begun reshaping their R&D business models by (i) streamlining operational activities and decision-making,[p20],[p21],[p22] (ii) rethinking the logic of value creation through more external R&D,[p23] (iii) including orphan drug development in their value creation process[p24] and (iv) redefining innovation itself — specifically how 'innovation' is defined and what level of innovation is considered appropriate for value capturing.

First, companies such as Pfizer, Bristol-Myers Squibb (BMS) and AstraZeneca have optimized their decision-making criteria and R&D processes in ways that have enabled them to increase the efficiency of their R&D organizations.[p20],[p21],[p22] Second, many leading pharma companies have developed their logic of value creation from the traditional fully integrated pharma company (FIPCO) model to one centered on the integration of external assets as a core strategy for innovation.[p23],[p25],[p26] For example, between 2015 and 2021, leading pharmaceutical companies sponsored 138 newly FDA-approved drugs, of which 65% originated from external sources, whereas only 28% were discovered and developed in-house.[p26] This shift marks their transition to a biotech-leveraged pharma company (BIPCO) model.[p26] Third, between 2014 and 2023, the FDA approved 229 orphan drugs across the industry, of which 105 were sponsored by the top 20 pharmaceutical companies.[p17] By contrast, some companies have redefined the R&D concept and degree of innovation for themselves, prioritizing lifecycle management over new drug development. For these companies, value capture is more effectively achieved by extending the commercial potential of established therapies – typically blockbusters – rather than relying solely on a high number of new drug approvals as the foundation of their R&D strategy. This approach leverages the potential not only of traditional blockbusters but also of 'niche busters'[p27] and, ideally, fully exploits mega blockbusters commercially through broad line extensions and other lifecycle management activities.[p13] Within the immunology and inflammation space, Humira® (adalimumab, AbbVie) exemplifies this approach, whereas Keytruda® (pembrolizumab, Merck & Co.) serves as a successful example in the category of oncology. This strategic shift reflects the

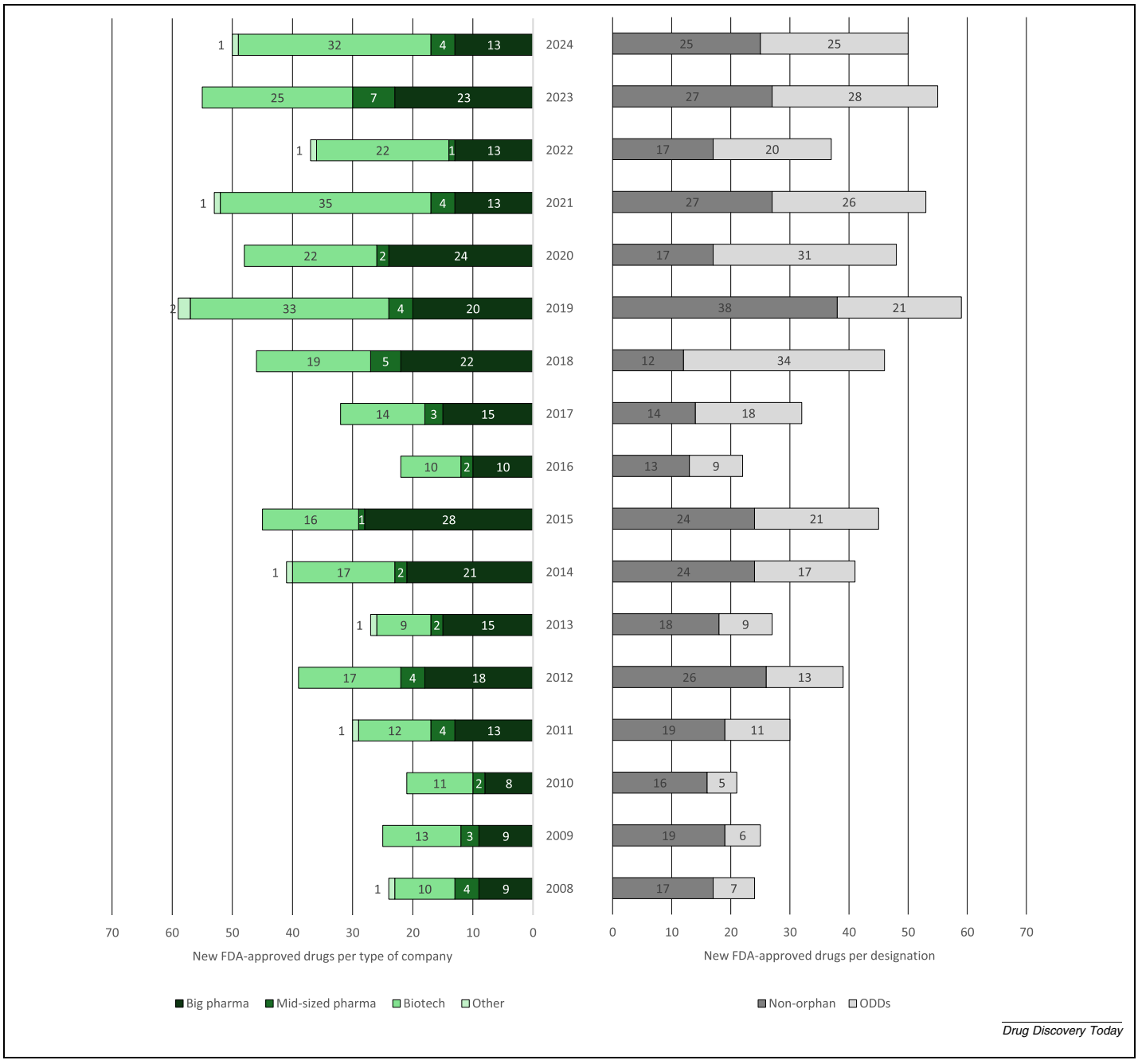

FIGURE 1

FDA-approved new drugs by type of company and designation (2008–2024). New molecular entities (NMEs) and new therapeutic biologics (NTBs) approved by the FDA's Center for Drug Evaluation and Research (CDER) by year (split according to company type and drug designation), orphan drug designation (ODD) versus non-ODD. Big pharma refers to companies that belong to the group of leading pharmaceutical firms (top 20 by total revenues 2024); mid-sized pharma are smaller (non-top 20) pharmaceutical companies; biotech (biotech innovator) are those firms that were founded after 1976 and do not belong to the group of big pharma. The 'others' category includes organizations and public institutions whose business model does not typically correspond to that of a research-based pharmaceutical or biotech company. *Data Source:* novel drug approvals at FDA (https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda) supplemented by authors' own data.

understanding that, although value creation comes from an efficient R&D organization, value capturing is primarily driven by individual assets – with mega-blockbusters playing a crucial part in ensuring financial stability.[p28]

R&D productivity and the biopharmaceutical ecosystem

An ecosystem can be defined as a network of interdependent and heterogenous actors where activities mutually impact one another.[p29],[p30] In line with extended definitions,[p31],[p32] the biopharmaceutical ecosystem can be understood as a complex innovation network that integrates all relevant actors – industry, investors, public research institutions, regulatory agencies and policymakers –

together with the economic dynamics and interdependencies among them, functioning in a symbiotic manner to advance biomedical science and technology, drive innovation, as well as enable the discovery and development of new drugs. Here, value creation (the process of generating value) and value capture (the process of securing returns from value creation) are fundamental activities of the companies involved.[p33]

In this context, although companies in the biopharmaceutical ecosystem differ in terms of purpose, positioning, therapeutic modalities, therapeutic areas or the use of open versus closed R&D approaches, they can be categorized according to their value creation and capture mechanisms and fundamentally be divided into four categories: (i) big pharma companies, (ii) mid-sized pharma firms, (iii) biotech innovators and (iv) service providers. Although the fundamental industry conditions, such as regulatory and quality standards or technology intensity, impact all companies regardless of their size and scope, we argue that the various categories are not equally affected by the R&D productivity challenge. For instance, biotech innovators, that often adopt a royalty income pharma company (RIPCO) or platform-based business model,[p34] typically do not operate across the full value chain from drug discovery to commercialization. Instead, they focus on developing technology platforms or lead assets (value creation) with the intent to license or sell them to large pharmaceutical companies (value capture). Biotech innovators are often constrained by limited resources – financial capital and drug development capabilities – and rely financially either on volatile public markets (public biotech) or venture capital funding (private biotech). Additionally, the scalability of novel therapeutic modalities, such as cell and gene therapy, poses a significant challenge to growing into fully integrated, large-scale operations. More specifically, given their resource limitations, the growing complexity of biomedical science and investor expectations for a timely exit, many biotech firms position themselves as strategic partners for big pharma, thereby becoming an integral part of the value creation networks of leading companies.[p26],[p35],[p36] In 2024 alone, the industry recorded 136 M&A deals and 771 partnerships between pharma and biotech firms,[p37] which highlights the close collaboration of biotech firms, biotech investors and pharmaceutical companies in the biopharmaceutical ecosystem. Thus, we argue that, with regard to the positioning of biotech and particularly the way in which biotech creates and captures value, their priority remains on financing drug research and strategically collaborating with big pharma, rather than tackling the broader issue of R&D productivity.

Mid-sized pharma companies find themselves stuck in the middle – they lack the scale and resources needed to sustain an end-to-end integrated business model, while being too large to operate solely as cost-efficient biotech innovators. Although, like all research-based companies, they are negatively affected by the enormous costs of drug research, their primary challenge is not R&D efficiency itself, because their R&D pipelines are typically small. Rather, the main challenge for them is the financial sustainability of a research-driven business model. Specifically, whether they can secure R&D funding and competitive capabilities to cope with the increasing complexities of drug R&D. With cost estimates exceeding US$2.6B per new drug,[p10],[p11],[p19] it becomes evident that mid-sized companies can no longer maintain a business model based purely on R&D, as is seen with big pharma. As a result, they are left with two fundamental options: (i) to position themselves as niche specialists, such as Vertex Pharmaceuticals or Ipsen Pharma, that focus on rare diseases, where the emphasis is probably placed more on value creation than value capturing, as would be expected in a more competitive mature market segment; or (ii) to exit the market entirely, as demonstrated by ALTANA Pharma, which merged with Nycomed in 2006 and was later acquired by Takeda in 2012, after failing to develop a commercially successful successor to the blockbuster pantoprazole.

Service providers, such as research service companies or clinical research organizations (CROs),[p34],[p38] emerged in the 1980s and 1990s and have increasingly taken over parts of the value creation process of leading companies, such as toxicology studies or clinical trial operations. In doing so, they support big pharma companies in improving R&D efficiency by outsourcing parts of the value chain at lower cost and with greater flexibility, particularly in view of the high technical risks and planning uncertainties in drug R&D.[p39],[p40] This, in turn, allows leading companies to large-scale outsource while focusing internal resources on those segments of the value chain that are crucial to maintaining their competitive advantage.

Contract development and manufacturing organizations (CDMOs) also operate at a small segment of the value chain and create value not only by providing quality services but also specifically by hedging strategic risk, taking on the high investment costs of production facilities – often hundreds of millions of US$ – which originator companies typically cannot justify owing to small R&D pipelines and low success rates of individual R&D projects. This makes them, like CROs, an integral part of the value creation network of leading companies. However, when a major drug succeeds, as seen with the recent GLP-1 boom, these investments become viable. For instance, Novo Nordisk acquired Catalent for US$19B and is investing US$4.1B to expand production for Ozempic® and Wegovy®.[p41] Similarly, Eli Lilly plans to invest US$27B in manufacturing facilities driven by the success of Mounjaro®.[p42]

In contrast to the categories mentioned above, the challenge of R&D productivity puts end-to-end integrated pharma companies under constant pressure to manage (i) large R&D organizations, where economy of scale plays a role,[p11] and (ii) broad and diverse project portfolios,[p43] to ensure a steady R&D output. In addition, they must increasingly rely on external innovation,[p44] because internal R&D alone cannot guarantee the required steady stream of new drugs. Specifically, given their annual multi-billion-dollar R&D investments, big pharma investors place significant pressure on these companies to ensure R&D efficiency (an appropriate ratio of R&D expenditure to new drug approvals) and R&D effectiveness (a high level of commercial success relative to R&D investments). This in turn influences the evolution of business models toward maximizing R&D productivity: big pharma's business model sustainability depends on continuously launching high-selling drugs or maintaining mega blockbusters,[p28],[p45] because these drugs are

essential to finance large R&D infrastructures, cover drug development costs and fund the costly M&As required for value creation and value capturing.[p45]

Concluding remarks and future perspectives: is R&D productivity ultimately just a big pharma problem?

In our view, only the largest pharmaceutical companies operate a well-established, end-to-end integrated business model (FIPCO or BIPCO) and are therefore directly and fully affected by the R&D productivity challenge. Given their orientation toward growth through innovation, these companies typically (i) follow a first-in-class strategy,[p46] which requires them to (ii) leverage new science, (iii) take the inherent risk of drug research, (iv) commit substantial resources to drug development, (v) finance R&D expenditures over very long timelines and (vi) secure growth through the launch of new drugs, whether internally discovered or externally acquired. Consequently, they must address the dual challenge of maximizing R&D efficiency and effectiveness to ensure business sustainability, as evidenced by big pharma's adaptation of business models and numerous initiatives to enhance R&D performance.[p20],[p21],[p22],[p26],[p47]

Biotech innovators and other research-based firms often fail to reach the stage where optimizing R&D efficiency along the entire value chain or aligning business models toward R&D effectiveness becomes relevant, because they operate in smaller parts of R&D or assume different roles in the ecosystem. Instead, they prioritize different issues at the top of their agendas. Still, financial indicators can suggest a different picture: for instance, a study on investor returns showed that pharmaceutical companies (1980–2015) outperformed biotech firms.[p48] Second, biotech innovators, with fewer pipeline assets, are less able to absorb failures than big pharma, making them more vulnerable to business failure. Third, since the COVID-19 pandemic, the NASDAQ Biotech Index has also declined more sharply than the NYSE Arca Pharmaceutical Index, suggesting that R&D productivity pressures weigh more heavily on early-stage biotech than on big pharma. In our view, these financial indicators mentioned could be related to R&D productivity; however, it is more likely that additional factors influence the valuation of start-ups.[p49]

On closer assessment, one could even argue that they benefit from the R&D productivity challenge faced by the leading companies, because they are part of their value creation process. In this sense, the success of big pharma is contingent upon the contributions of other ecosystem actors, with all actors being interconnected through a dynamic process of mutual co-evolution.[p30]

- For instance, biotech innovators benefit from large pharmaceutical companies' need to manage the high complexity of science and technology, to fill R&D pipeline gaps and address product portfolio issues. Thus, biotech companies view big pharma as a source of financing,[p50] exemplified by licensing deals, equity investments or acquisitions – with big pharma serving as an exit strategy option for biotech innovators and investors.
- To offset enormous R&D investments, leading companies target market segments with the highest commercial potential, leaving gaps that mid-sized firms can fill through non-competitive niche (specialty) strategies or low-risk me-too approaches[p51] that build on big pharma's costly successes and failures.
- CROs and CDMOs benefit from the need of leading pharmaceutical companies to focus their resources on key elements of the value chain. Especially in light of the very low success rates and long timelines in R&D, service providers take on important roles in improving efficiency and minimizing risk throughout the R&D process.

Following this line of reasoning, the R&D productivity challenge has not only shaped the strategies of leading pharmaceutical companies over the past 20 years, driving most of them to adopt BIPCO models, but has also transformed the entire industry. It has created today's interconnected biopharmaceutical ecosystem, with big pharma at its center, bearing the highest risks due to its substantial R&D investments and facing constant pressure to generate high returns, thereby becoming locked into a cycle of continuous optimization of R&D productivity. Other actors support big pharma in improving its R&D efficiency and are thus involved in its value creation, while they most often depend on its performance and success. From this, it can be concluded that R&D productivity remains a universal challenge in the biopharmaceutical ecosystem, although it has the most fundamental impact on big pharma.

CRediT authorship contribution statement

Alexander Schuhmacher: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Oliver Gassmann:** Writing – review & editing, Writing – original draft. **Sebastian Kwisda:** Writing – review & editing, Writing – original draft. **Malte Kremer:** Writing – review & editing. **Markus Hinder:** Writing – review & editing, Writing – original draft. **Dominik Hartl:** Writing – review & editing, Writing – original draft, Conceptualization.

Data availability

Data will be made available on request.

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