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Benchmarking R&D success rates of leading pharmaceutical companies: an empirical analysis of FDA approvals (2006–2022)

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Previous analyses provide an industry benchmark of ~10% for the success rate in clinical development. However, prior analyses were limited by a narrow timeframe, a diverse research focus, biases in phase-to-phase transition methodology or a focus on specific use cases. We calculated unbiased input:output ratios (Phase I to FDA new drug approval) to analyze the likelihood of first approval using data from clinicaltrials.gov, encompassing a total of 2092 active ingredients, 19 927 clinical trials conducted by 18 leading pharmaceutical companies (2006–2022) and 274 new drug approvals. Our study reveals an average likelihood of first approval rate of 14.3% across leading research-based pharmaceutical companies, broadly ranging from 8% to 23%.

Keywords: Pharma; R&D; drug development; clinical development; clinical trials; likelihood of approval; success rate; R&D productivity

Introduction

The productivity of R&D in the pharmaceutical industry has been a topic of intense discussion for more than two decades.[(p1),(p2),(p3)] A key issue for companies is that investments in R&D are in an economically unsustainable ratio to the number of new drugs. As a result, some leading pharmaceutical companies have struggled to generate growth solely through internal R&D.[(p4),(p5)] Instead, major pharmaceutical companies have evolved their business models in R&D and obtained a large portion (65%) of their new drugs approved by the FDA from external sources, primarily biotech firms (2015–2021). This paradigm shift has led to the current business model of most leading pharmaceutical companies being referred to as 'biotech-leveraged pharma companies' (BIPCO).[(p5)]

The underlying metrics of poor R&D productivity include an R&D efficiency of US$6.1B R&D investment (R&D input)

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per new drug (R&D output),[p4] very long timelines from the initial idea of a new therapeutic approach to the launch of a new drug with an average of 14 years[p1] and low success rates in the drug discovery and development stages.[p1] Particularly, early clinical development has been identified as the most important determinant for R&D efficiency and is therefore considered as a bottleneck in drug development.[p2],[p6]

In general, clinical-stage drug development is organized in a gated process of three distinct clinical trial phases (Phase I, Phase II, Phase III) with a development time of 8–10 years from a first-in-human (FiH) study to drug approval and marketing authorization by the FDA.[p1] Previous analyses, which have included a wide range of indications and study subjects, have revealed diverse results for the overall success rate of clinical development (Phase I to drug approval), ranging from <7% to >25%, with the commonly cited figure of ~10%.[p2],[p6],[p7],[p8],[p9],[p10],[p11] The overall success rate is often referred to as the probability of technical and regulatory success (PTRS) or likelihood of approval (LoA). It represents the probability that a drug candidate fulfills its sponsor-defined efficacy, safety and market benchmarks, typically defined in the target product profile (TPP), while also meeting the regulatory agency's approval standards, such as those of the FDA's Center for Drug Evaluation and Research (CDER).

LoA studies typically calculate the PTRS based on phase-to-phase transitions in R&D, analyzing assets from various companies, including biotech and pharmaceutical firms. These studies often determine success rates for each phase and, in some cases, probabilities associated with therapeutic areas or modalities. For instance, analyzing oncological products approved by the top 20 pharmaceutical companies between 1990 and 2005, clinical phase transition probabilities were found to be 76.8% from Phase I to Phase II, 59.4% from Phase II to Phase III and 57.1% from Phase III to approval. This results in an overall LoA of ~26.1% from the start of Phase I to approval – an exceptionally high success rate, which was not confirmed in subsequent analyses.[p11] In a 2014 analysis, including data (from 2003 to 2011) from 835 companies (predominantly biotech firms) and 4451 compounds, the LoA across clinical development phases was found to be 10.4%. The success rates per phase were as follows: Phase I to Phase II at 64%; Phase II to Phase III at 32%; Phase III to new drug application (NDA) at 60%; and NDA to approval at 83%.[p9] In another analysis, using data from Biomedtracker (1 Jan 2011 to 30 Nov 2020) of 12 728 clinical and regulatory phase transitions across 9704 clinical drug development programs from 1779 biopharmaceutical companies, success rates were averaged as follows: 52.0% from Phase I to Phase II; 28.9% from Phase II to Phase III; 57.8% from Phase III to NDA/biologic license application (BLA); and 90.6% from NDA/BLA to approval, resulting in an LoA of 7.9%.[p7] A recent analysis, focusing on R&D productivity of 14 major pharmaceutical companies (2018–2022), revealed a clinical success rate of 10.8% across all therapeutic areas.[p2]

Given the variability, inherent limitations and biases of previous LoA studies, such as those related to period of investigation, or sampling, measurement and reporting biases, a current benchmarking analysis is needed to yield robust and timely results on LoA rates in the pharmaceutical industry. Because success rate data are used for benchmarking analyses, project planning or internal rate of return (IRR) analyses, the reliability and traceability of the data are crucial. For this reason, we decided to calculate the LoA rate over a longer time-period and based on a coherent and reliable dataset. In this context, coherent and reliable means that the companies have comparable business models in R&D, existed throughout the entire observation period, demonstrated consistently successful R&D activities during that time and considered clinical development a core R&D capability, ensuring that the data hold relevance beyond the specific research subject.

Thus, the scope of this study was to analyze LoA rates of the top 20 pharmaceutical companies globally, which fulfil the above-mentioned inclusion criteria. The objective was to analyze their LoA rates and draw conclusions relevant to the companies and the industry. In fact, we were able to analyze the LoA rates for 18 leading pharmaceutical companies (2006–2022) using publicly available data from clinicaltrials.gov, encompassing 2092 distinct assets (active ingredients), 19 927 clinical trials (Phase I to Phase III) and 274 new drugs approved by the FDA (for methodological details see supplementary material S1 available online). We calculated unbiased input:output ratios to assess the number of initiated Phase I trials per new asset in relation to the number of new drug approvals by the CDER.[p12],[p13],[p14],[p15],[p16],[p17],[p18],[p19],[p20],[p21],[p22],[p23],[p24],[p25],[p26],[p27],[p28] We further assessed the total number of Phase I, Phase II and Phase III trials and calculated the Phase I:Phase III ratio for each company to better understand their R&D paradigms.

Likelihood of first approvals and R&D paradigms

Between 2006 and 2022, the analyzed companies developed a total of 2092 active ingredients by conducting 19 927 clinical trials, which are distributed in the gated process as follows: Phase I – 8281; Phase II – 5455; and Phase III – 6191 (Table 1). On average, each pharmaceutical company worked on 116 assets in clinical development, conducting 460 Phase I, 303 Phase II and 344 Phase III studies and receiving 15 FDA approvals (0.9 per year). Collectively, this effort resulted in 274 FDA-approved new drugs from the 18 leading pharmaceutical companies.

On a company level, the following numbers were observed (Table 1). Pfizer (234), Roche (234) and GSK (187) tested significantly more active ingredients than other companies, such as Astellas (58), Eisai (38) or Novo Nordisk (29). Similarly, there was a significant variation in the number of clinical trials conducted with Pfizer (2215), GSK (2204) and Novartis (1826) reporting far more clinical trials compared with companies such as Amgen (507), Gilead (457) or Eisai (349).

We used the compiled data to (i) calculate the LoA rate per firm, (ii) calculate the average LoA rate of the group of 18 leading companies, which, owing to the significance of these companies, could also serve

as an indicator for the entire industry, and (iii) illustrate the strategic positioning of these companies regarding their clinical activities. Specifically, our results reveal the following key insights:

(i) The average likelihood of first approval rate (2006–2022) across the 18 leading pharmaceutical companies was 14.3% (median 13.8%).
(ii) Among the companies analyzed, the LoA rates broadly ranged from Abbvie (8.1%), Astellas (8.6%) and GSK (9.1%) to Eisai (18.4%), Novo Nordisk (20.7%) and Amgen (22.8%) (Table 1).
(iii) There are two contrasting R&D paradigms, characterized by a focus on either early-stage (Phase I) or late-stage (Phase III) development activities (Figure 1). Whereas Sanofi (0.50), Gilead Sciences (0.53), Takeda (0.55), Novartis (0.59) and AbbVie (0.79) had relative low Phase I:Phase III ratios, Astellas (1.76), Johnson & Johnson (1.87), Pfizer (1.94), BMS (2.06), Eisai (2.19) and Boehringer Ingelheim (3.06) are characterized by significantly higher Phase I:Phase III ratios.

Limitations

Our analysis has several limitations that should be taken into account for proper data interpretation. First, our linear input-to-output approach was not capable of capturing parallel indication expansion paths (such as several Phase II trials conducted per drug candidate or asset) or line extension approvals, thereby lowering the calculated LoA for pharmaceutical companies focusing on these drug development paths, as discussed below in more detail. Second, our point-in-time analysis could not correct for clinical trials that were overlapping (ongoing, actively recruiting) with the start (2006) or the end (2022) of our overall assessment period. Third, whereas our approach included internal and external assets, in-licensed or acquired assets could only be assigned to the relevant big pharma sponsor if clinicaltrials.gov datasets were updated accordingly. Fourth, our public-domain-based analysis relied on the quantity and quality of clinicaltrials.gov data, which are entered by default by clinical trial sponsors and are not cross-checked or validated externally. By extracting data from 19 927 clinical trials, we noticed significant differences across sponsors and clinical trial phases. Although datasets were overall richer for late-stage trials, Phase I clinicaltrials.gov entries tend to be reduced to a minimum of information, an approach to limit competitively sensitive information being available at early-stage development. Owing to this lack of granularity, our method was unable to reliably differentiate between Merck & Co (Merck MSD) and Merck KGaA as distinct entities, therefore these two companies were excluded from our analysis. Sixth, we should note that clinicaltrials.gov is mandatory for studies conducted in the USA. Seventh, it is standard practice for leading companies to register all their studies on this platform. Because our analysis of LoA rates is based on the ratio of the first Phase I study to FDA drug approval, we might potentially overlook individual Phase I studies conducted prior to the first Phase I study registered in the USA. Therefore, although this is unlikely, it is important to acknowledge that our analysis could potentially exclude individual Phase I studies conducted before the first Phase I study registered on clinicaltrials.gov. Another inherent limitation of our broad input-to-output analysis approach is the lack of details on underlying factors contributing to clinical success

TABLE 1

Compilation of clinical development activities of leading pharmaceutical companies (2006–2022)

Sponsor	Total IDs	Phase I	Phase II	Phase III	PhI:PhIII ratio	Total clin trials	New drugs	LoA (%)
AbbVie	86	192	131	244	0.79	567	7	8.14
Amgen	95	180	150	177	1.02	507	13	22.81
Astellas	58	288	148	164	1.76	600	5	8.62
AstraZeneca	129	770	336	491	1.57	1597	17	13.18
Bayer	82	298	202	264	1.13	764	14	17.07
BI	59	812	222	265	3.06	1299	8	13.56
BMS	164	510	392	248	2.06	1150	23	14.02
Eisai	38	162	113	74	2.19	349	7	18.42
Eli Lilly	108	558	321	338	1.65	1217	12	11.11
Gilead	82	97	204	156	0.53	457	14	17.07
GSK	187	935	646	623	1.50	2204	17	9.09
Roche	234	525	466	472	1.11	1463	27	11.54
J&J	143	651	297	349	1.87	1297	21	14.69
Novartis	174	412	720	694	0.59	1826	29	16.67
Novo	29	352	82	257	1.37	691	6	20.69
Pfizer	234	1123	514	578	1.94	2215	27	11.54
Sanofi	128	227	320	455	0.50	1002	17	13.28
Takeda	62	189	191	342	0.55	722	10	16.13
Total	**2092**	**8281**	**5455**	**6191**		**19 927**	**274**	
Mean	**116**	**460**	**303**	**344**	**1.40**	**1107**	**15**	**14.31**

The data compilation includes the number of new active substances (IDs) studied in clinical trials (2006–2022), the number of clinical trials per company and phase, the Phase I:Phase III ratios, the number of new drugs approved by the FDA per company and the resulting likelihood of approval (LoA) of leading pharmaceutical companies (also during 2006–2022).
Data source: clinicaltrials.gov and FDA homepage. Abbreviations: BI, Boehringer Ingelheim; BMS, Bristol Myers Squibb; GSK, GlaxoSmithKline; J&J, Johnson & Johnson; ID, new active ingredient tested in clinical trials.

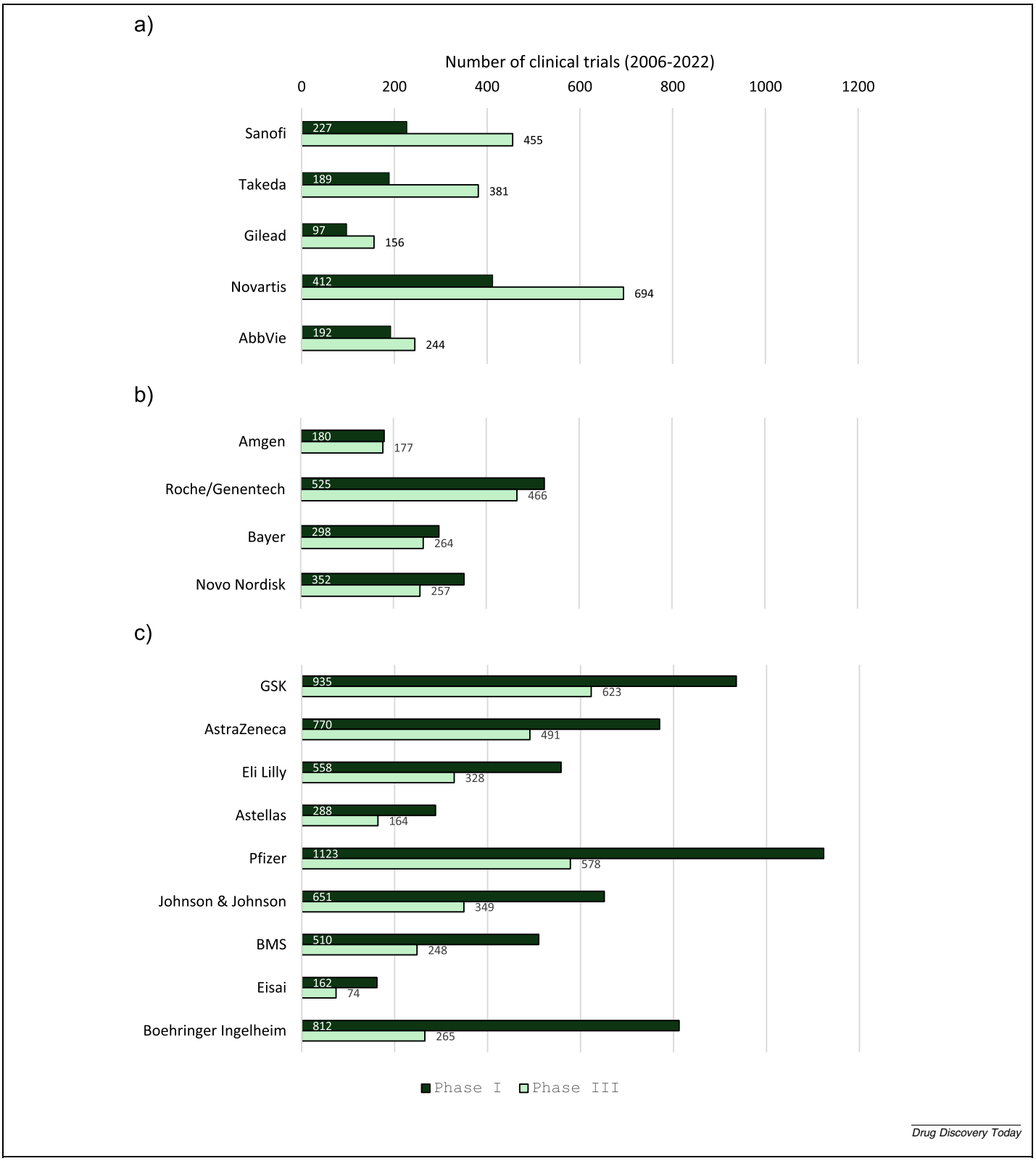

FIGURE 1

Number of clinical trials (Phase I and III) of leading pharmaceutical companies (2006–2022). **(a)** Companies with Phase I:Phase III ratio <1. **(b)** Companies with Phase I:Phase III ratio of 1–1.5. **(c)** Companies with Phase I:Phase III ratio >1.5. Data Source: clinicaltrials.gov, Abbreviations: BMS, Bristol Myers Squibb; GSK, GlaxoSmithKline.

rates, such as drug modality, therapeutic area or lead indication status, which were identified based on previous analyses.[p6],[p9],[p10] Importantly, individual therapeutic areas have different LoA rates and companies vary significantly with regard to therapeutic area breadth, which limits our cross-company LoA comparability.

Concluding remarks and discussion

Because the leading pharmaceutical companies examined here are under significant pressure to improve their R&D productivity,[p4] it is especially important for these companies to have access to current and reliable LoA data. Although the leading pharmaceutical companies operate with business models distinct from those of specialty pharma or biotech firms, analyzing their LoA rates remains broadly relevant, because the top companies included in this analysis represent a substantial share of recent new drug approvals and the global prescription drug market.[p29]

To provide a current and unbiased benchmark of the LoA rate, we performed an R&D input-to-output analysis of assets that entered clinical development between 2006 and 2022 and that resulted in new drug approvals by the CDER. To minimize sampling biases and in contrast to previous studies, which included the heterogenous market segment of biotech companies to obtain a sufficiently large sample size, we analyzed 2092 assets and 19 927 clinical trials from the homogenous group of 18 leading pharmaceutical companies.

Our analysis focused on the leading pharmaceutical companies, which are experienced in clinical drug development and constantly refine their strategies to improve LoA rates, as highlighted by Pfizer's investigations and implemented actions on clinical R&D productivity and AstraZeneca's 5R framework on R&D productivity.[p30],[p31] This provided reliable, relevant and representative datasets across large pharmaceutical companies. Because external factors, such as regulatory changes or pandemics, can temporarily impact clinical development, we used a large dataset over an extended period (2006–2022) to draw reliable conclusions across the pharmaceutical industry.

Our analysis applied an end-to-end (R&D input-to-output) approach avoiding phase-specific progression bias (reporting bias) that might happen if the analysis estimates LoA rates as the result of individual phase transition probabilities. In addition, the reliability of previous clinical success analyses might be limited owing to potential measurement biases, because they either covered shorter timeframes or calculated success rates per trial phase separately and sequentially, which provides higher granularity for each trial phase, but fails to capture seamless (Phase I/Phase II, Phase II/Phase III) and phase-skipping (Phase I $\geq$ Phase III) trials that became more popular within the past decade. Compared with previous studies, our analysis yielded an average LoA rate of 14.3% for the leading companies, which covered all 2092 active ingredients developed by the 18 leading companies and the related 274 new drug approvals (2006–2022). Owing to the significance of the 18 companies, the 14.3% (median 13.8%) could also serve as an indicator and benchmark for the entire industry.

What are potential explanations for the fact that the LoA rate we identified is higher than most recent LoA rates? Importantly, our analysis included only linear Phase I to first drug approval rates and did not capture multiple and/or parallel indication approval paths, line extension approvals, new formulation approvals (such as subcutaneous formulations) or pediatric approvals, which decreases the overall LoA calculated for companies with a focus on these lifecycle management paths. A prototypic company included in our analysis typically pursuing these kinds of indication expansion or line extension approaches is Abbvie with Humira® being approved for eight adult and four pediatric or juvenile indications, which might explain the low LoA calculated for Abbvie in this analysis, contrasted by the remarkable commercial success of this pharmaceutical company. Viewing these factors in combination, strategic drug lifecycle management (LCM), including broad indication expansion, line extensions and pediatric development paths (one-target-multiple-indications paradigm),[p32] might be commercially highly attractive without the risk of pan-clinical phase attrition. Because the US Inflation Reduction Act (IRA), however, disincentivizes line extension strategies by rendering those commercially less attractive, first drug approval rates will probably gain more impact for future R&D frameworks.

We identified a significant variation in LoA rates among the companies analyzed, with Abbvie demonstrating the lowest rate at 8.14% and Amgen achieving the highest at 22.81%. What insights do these numbers provide regarding the success of the leading pharmaceutical companies? First, these numbers reflect the probability of success in developing new assets and obtaining market approval. At the same time, second, these discrepancies can be explained by different R&D strategies employed by the companies in clinical development, such as risk appetite, indication focus or portfolio breadth. Third, these results should be viewed in a broader context, especially considering R&D efficiency and R&D effectiveness. Specifically, this means that R&D output (R&D success) does not necessarily translate into commercial success, and some companies might prioritize R&D outcome over output of their R&D organizations. For example, Abbvie had the lowest LoA (8.14%, 2006–2022) among the companies analyzed yet, during the same period, Abbvie benefited from the commercially most successful blockbuster: Humira®, which reached total sales of nearly US$200B (2002–2023). Single blockbusters, rather than the quantity of low-success-assets, have the greatest impact on R&D outcome.[p33],[p34]

Regarding the R&D strategy, which typically defines how a company leverages its R&D resources to create and sustain a competitive advantage, we observed two distinct paradigms in the Phase I:Phase III ratios – companies focused on early clinical development and those focused on late-phase development. Although these two approaches are not empirically proven, it is important to note that these contrasting paradigms can result from different R&D strategies. Pharmaceutical companies with a low Phase I:Phase III ratio (i.e., Sanofi, Gilead, Novartis, Takeda, Amgen and Abbvie) probably focus on a few high-priority Phase I assets with broad mechanism-of-action (e.g., anti-inflammatory assets) that are sequentially expanded into multiple Phase III indications. This asset-centric, basket-like approach is exemplified by Humira®

(Abbvie) or Cosentyx® (Novartis). Companies with a high Phase I:Phase III ratio, such as Boehringer Ingelheim, Eisai, Bristol-Myers Squibb, Astellas, Johnson & Johnson or Pfizer, test multiple compounds in Phase I and probably advance only prioritized drug candidates into late-stage Phase III trials (early decision making: dropping losers/accelerating winners). This portfolio approach is exemplified by Pfizer's 'signs of clinical activity' (SOCA) R&D productivity paradigm.[p31]

Beyond such aspects, R&D strategy also defines how clinical development is organized. The two prevalent models currently observed in the industry are: (i) a unified structure, with a single clinical development unit; and (ii) a modular structure, which separates early (Phase I/Phase IIa) from late (Phase IIb/Phase III) clinical development. Whereas both organizational concepts have their up- and downsides, modular setups bear the inherent risk of fragmentation, misalignment and project delays. However, further dedicated analyses are necessary to assess the impact of these organizational models on clinical success rates.

Future outlook

LoA rates are highly valuable data for research-based pharma companies in benchmarking, R&D project management, portfolio simulations, resource allocation and portfolio decisions. Our comprehensive analysis provides reliable data to support these efforts. Disregarding any outliers,[p11] the average LoA rate for clinical development from studies in recent years is ~10%.[p2],[p6],[p9],[p10] Thus, it remains to be addressed what the herein analyzed 14.3% LoA means in practice. Generally speaking, a 14.3% LoA in drug development for big pharma is significantly higher than the 10% success rate typically discussed in the literature and primarily based on data from biotech companies. One possible explanation, beyond differences in the setups of various analyses, might be that smaller companies, such as biotech firms, operate with fewer development capabilities, limitations in their assets or business models that involve a higher risk appetite, which can lead to lower success rates in development. Nevertheless, when examined closely, the 14.3% LoA is far too low for R&D productivity to serve as a foundation for a sustainable business model in R&D for big pharma. This analysis once again underscores that R&D productivity, with underlying parameters such as LoA, continues to call into question the long-term success prospects of research-driven pharmaceutical companies. Leading companies are still tasked with addressing the R&D productivity challenge and developing solutions in this regard. One emerging solution in recent years has been the application of AI in drug development to make the development process more efficient. Digital tools such as patient recruitment platforms, virtual trials, digital biomarkers, real-world evidence and *in silico* clinical trials provide the opportunity to significantly decrease dependency on costly *in vivo* studies, enabling the industry to transform R&D into an economically sustainable value creation process.[p35],[p36],[p37],[p38]

CRediT authorship contribution statement

Alexander Schuhmacher: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Markus Hinder:** Writing – review & editing, Writing – original draft. **Elazar Brief:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Oliver Gassmann:** Writing – review & editing, Writing – original draft. **Dominik Hartl:** Writing – review & editing, Writing – original draft, Visualization.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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