Universidade de Lisboa

Faculdade de Farmácia

Pharmaceutical Innovation in Healthcare:

Exploring Open Innovation Models and Biotechnology

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Monografia orientada pela Professora Doutora Ana Catarina Beco Pinto Reis, Professora Auxiliar com Agregação da Faculdade de Farmácia da Universidade de Lisboa, e coorientada pelo Professor Doutor António Carvalho Pais, Doutorado e Mestre em Filosofia pela Faculdade de Ciências Sociais e Humanas da Universidade NOVA de Lisboa

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Acknowledgments

As I reflect on the journey of developing this thesis, I am filled with gratitude and excitement for the invaluable knowledge I have acquired in a field that captivates my curiosity. I want to thank my family for providing the conditions that made my studies possible, my friends for their unwavering encouragement, and my professors for their insightful guidance throughout this process. Finally, I would like to acknowledge my determination and resilience, which propelled me forward in pursuing this work.

Driven by what I've learned, I look forward with confidence.

Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

A produtividade em Inovação e Desenvolvimento (I&D) na Indústria Farmacêutica enfrentou um declínio constante entre 2010 e 2019, com o custo de desenvolver um novo medicamento a disparar para 2,3 mil milhões de dólares. Levar um novo medicamento ao mercado demora tipicamente entre 10 e 15 anos, e a realidade é implacável: mais de 96% dos projetos falham. No entanto, apesar destes obstáculos, a indústria continua a prosperar, graças à evolução dos modelos de negócio e a uma crescente adoção de estratégias de *Open Innovation*.

A colaboração tornou-se uma "tábua de salvação" para superar desafios de produtividade e eficiência. As empresas biofarmacêuticas recorrem cada vez mais à inovação por fontes externas para preencher lacunas científicas, aleando métodos tradicionais com novas abordagens para otimizar a I&D. Os modelos de O*pen Innovation* — incluindo *Outsourcing*, parcerias estratégicas, fusões e aquisições, I*n-licensing* e capital de risco corporativo — são agora essenciais para as empresas manterem-se competitivas e transformar ideias inovadoras em resultados em saúde. A Biotecnologia, outrora recebida com ceticismo, evoluiu ao longo dos últimos 50 anos para se tornar uma força importante na saúde. Em 2023, os medicamentos biológicos representavam 70% dos 20 medicamentos mais vendidos no mundo, ilustrando a sinergia entre os setores de biotecnologia e farmacêutico, a qual contribuiu de forma significativa para a melhoria do desenvolvimento de medicamentos.

Inovações recentes em biofarmacêuticos abrangem o espectro de "Diagnóstico-Prevenção-Tratamento", exemplificado pelo desenvolvimento de vacinas contra a COVID-19 e avanços em proteómica em contexto da descoberta de biomarcadores. Abordagens como *gene-modified cell therapy, RNA therapy,* e *oncolytic virotherapy* estão a ganhar terreno, particularmente em oncologia e neurologia, que juntas representam mais de 54% dos ensaios clínicos em 2023 e as áreas de maior investimento. A aprovação pela FDA do LEQEMBI para a doença de Alzheimer ilustra, por exemplo, o potencial das *startups* para desenvolver terapias inovadoras, apesar dos desafios inerentes resultando em 90% das startups acabarem por falhar, frequentemente devido a capacidades de gestão inadequadas e capital insuficiente — dois fatores críticos que influenciam o seu sucesso.

Assim, o objetivo desta tese é apresentar uma visão geral da inovação da indústria farmacêutica na saúde, examinando os papéis da O*pen Innovation* e da biotecnologia.

Palavras-chave: Indústria Farmacêutica, Biotecnologia, *Open Innovation,* Saúde, Startups.

Abstract

R&D productivity in the pharmaceutical industry steady declined from 2010 to 2019, with the cost of developing a new drug soaring to $2.3 billion. Bringing a new medicine to market typically takes 10 to 15 years, and the reality is stark: over 96% of drug development projects fail. Yet, despite these hurdles, the industry continues to thrive, thanks to evolving business models and a growing embrace of open innovation strategies.

Collaboration has become a lifeline for overcoming productivity and efficiency challenges. Biopharmaceutical companies increasingly turn to external innovation to fill scientific gaps, blending traditional methods with new approaches to streamline R&D. Open innovation models—including outsourcing, strategic partnerships, mergers and acquisitions, in-licensing, and corporate venture capital—are now essential for companies looking to stay competitive and turn innovative ideas into successful health solutions.

Biotechnology, once met with scepticism, has evolved over the past 50 years into a major force in healthcare. By 2023, biologics accounted for an impressive 70% of the top 20 best-selling drugs, demonstrating the synergy between biotech and pharmaceutical sectors that has significantly enhanced drug development.

Recent biopharmaceuticals innovations span the "Diagnosis-Prevention-Treatment" spectrum, exemplified by the rapid development of COVID-19 vaccines and advances in proteomics for biomarker discovery. Approaches like gene-modified cell therapy, RNA therapy, and oncolytic virotherapy are gaining momentum, particularly in oncology and neurology, which together represent over 54% of clinical trials in 2023 and the areas attracting most investment. The FDA's approval of LEQEMBI for Alzheimer’s disease illustrates the potential of biotech startups to deliver groundbreaking therapies despite inherent challenges resulting in 90% of biotech startups failure, often due to inadequate management capabilities and insufficient capital—two critical factors that influence their success.

Thus, the aim of this thesis is to provide an overview of pharmaceutical industry innovation in healthcare by examining the roles of open innovation and biotechnology.

Keywords: Pharmaceutical Industry, Biotechnology, Open Innovation, Healthcare, Startups

Abbreviations

AD - Alzheimer's disease

BLA - Biologics License Applications

BMS - Bristol Myers Squibb

CAGR - Compound Annual Growth Rate

CDMO/CMO - Contract Development and Manufacturing Organizations/Contract Manufacturing Organizations

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

CRO - Contract Research Organization

CTI - Centre for Therapeutic Innovation

CVC - Corporate Venture Capital

FGF - Fibroblast Growth Factors

FIC - First-in-Class

FIM - Friedrich Miescher Institute for Biomedical Research

FO - Follow-On

GSK - GlaxoSmithKline

HNSCC - Head and Neck Squamous Cell Carcinoma

HPV - Human Papillomavirus

IP - Intellectual Property

M&A -Mergers and Acquisitions

mAb - Monoclonal Antibody

MIT - Massachusetts Institute of Technology

NDA - New Drug Applications

NVF - Novartis Venture Fund

OECD - Organisation for Economic Co-operation and Development

OV - Oncolytic Virus’s

PPP - Public-Private Partnerships

PDUFA - Prescription Drug User Fee Act

R&D - Research and Development

rDNA - Recombinant DNA

ROI -Return on Investments

SCD - Sickle Cell Disease

SMEs - Small and Medium Enterprises

UIC - University-Industry Collaboration

VEGF - Vascular Endothelial Growth Factors

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1 Introduction

The pharmaceutical industry relies on significant investments to bring new drugs to market, mainly due to the highly complex process involving disease research, development of potential treatments, manufacturing methods, and rigorous testing for quality, safety and efficacy. (1) In 2022, health industries accounted for €261.4 billion (20.9%) of the €1,249.7 billion invested in research and development (R&D) by the top 2,500 global companies, making it the second most R&D-investment intensive sector. In particular, pharmaceutical companies contributed 167.3 billion (64%) of this total, while biotech companies contributed 66.5 billion (25.4%). Biotech's share of health industry R&D has been expanding significantly - from 15% of pharmaceuticals' R&D in 2012 to 39.8% in 2022 - highlighting its growing role in the sector. (2)

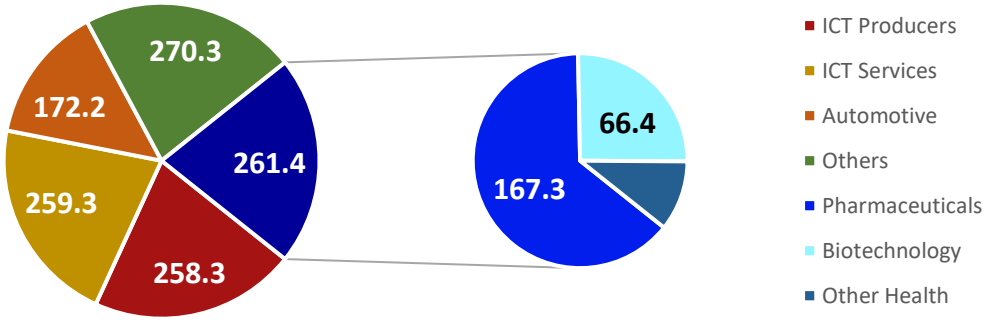

Figure 1. 2022 R&D investment by the top 4 sectors in EUR billions. The right pie with a total of 261.4 billion focuses on the Health Industries. Source: 20th edition of 'The EU Industrial Research & Development (R&D) Investment Scoreboard (2023)

Breakthroughs in drug discovery are uncommon, with innovation usually occurring incrementally. Development is considered uncertain and frequently hinges on inherently erratic breakthrough discoveries, which may or not lead to a cascade of further discoveries. (3) Typically, a new medicine takes 10 to 15 years to reach market, with an average of 8 years only to reach the clinical stage. (4) When a drug initiates phase I clinical trials, it faces a staggering average chance of receiving marketing approval of 14%, although this rate varies depending on the therapeutic area, drug type, approval process and others. (5) Unfortunately, over 96% of drug development projects ultimately fail, with 90% of these failures occurring at the clinical stage, which further highlights the costly, time-consuming, and uncertain nature of R&D. Failure rates are particularly high for drugs targeting novel mechanisms against previously "undruggable" proteins and for specific conditions like Alzheimer's disease (AD), where the

underlying pathophysiology remains poorly understood. (6,7) Nevertheless, biopharma industry's commitment to drug discovery and dedication to advance novel therapies did not slow down. This can be seen in clinical trial activity over the past 20 years, which has surged significantly, growing from 12,024 trials in 2004 to 506,666 in 2024 - an average annual increase of around 24,842 trials. (8)

Although there is no gold standard cost of bringing a new drug to market, this expense has risen significantly in the past three decades. (7) A survey of 10 large pharmaceutical companies revealed that this cost increased from $802 million in 2013 (considering drugs that entered clinical trials anyplace in the world between 1993-1994) to $2,558 million in 2016 (considering the period 1995-2007). (9) Proving this trend is Deloitte´s statistics on the R&D expenditure to progress a new drug from discovery to launch over a decade (2013-2023), which reports a 170% increase in costs rising from $1,296 million to $2,284 million. (10)

Deloitte's analysis shows that R&D productivity experienced a steady decline from 2010 to 2019. (5,11) Although there was a temporary boost in 2020 and 2021 due to the COVID-19 pandemic, productivity dropped again in 2022. Fortunately, signs of improvement began to emerge in 2023. This can be attributed to a complex combination of factors, including rising R&D costs, extended and more complex development cycles, imminent patent cliffs[1], a complex mergers and acquisitions (M&A) landscape, and constant changes in regulations. (10) R&D's opportunistic nature is other explanation for the decline. Since the most easily discovered ideas are taken advantage of first, and that new ideas become more difficult to find as information accumulate, the only way to maintain or boost output is to significantly increase research effort counteract falling productivity. (5)

When examining R&D productivity, a key indicator to consider is R&D efficiency, which examines how effectively resources are transformed into new drugs (input *versus* output) throughout the R&D process. Over 20 years (2001–2020), Alexander Schuhmacher (2023) studied a group of 16 leading research-based pharmaceutical companies further proving this trend. These companies showed a collective investment of $1.539.9 billion, with a significant increase in R&D spending from $249.7 billion (2001–2005) to $476.7 billion (2016–2020), meaning that all companies increased their R&D investment by 20% over 20 years. Over this period, they developed 251 new molecular entities and therapeutic biologics, which translates

[1] Patent cliff refers to a sharp decline in revenue or profitability when a companies' patents expire, opening them up to competition. (144)

to an average annual R&D expenditure of $4.4 billion per new drug. Despite an increase in the average annual output of new drugs, which rose from 9.1 during 2001–2010 to 15.7 from 2011 to 2020, the share of FDA-approved drugs by big pharma plummeted from 76% in 2001 to just 25% in 2020.

This decline resulted in pharma companies receiving only 0.78 FDA-approvals per year (2001 to 2020). The 251 new drugs launched made $1,796.4 billion in revenue, accounting for 25% of the total sales of the 16 companies studied. When calculated, the average R&D efficiency among the companies analysed was $6.16 billion per new drug, exceeding the estimated R&D cost per new molecular entity of $2.6–$2.9 billion by more than double. And, although, nearly half of these companies generate enough return on investment (ROI), 7 companies had to address their negative R&D efficiency through M&A and other business strategies. Additionally, 57% of new drug launches from 2011 to 2020 were unprofitable. (12)

Historically, “blockbuster drugs,” which include marketed drugs with over 1 billion annual sales potential, have been the pharmaceutical companies go-to financial strategy to sustain innovation-driven R&D models. Even though this model is proven to still be profitable, and that nearly a quarter of 2023-2025 launches are expected to become blockbusters, high pressures arise mainly from the loss of patent protection, which potentially can lead to poor strategic decisions such as expensive and/or risky M&A. (13,14)

Major branded drugs such as AbbVie's “Humira”, Merck & Co.'s “Keytruda”, and Johnson & Johnson's “Stelara” expect to face biosimilar competition within the next decade. (15) AbbVie's blockbuster anti-TNF immunology drug, Humira, that hit $19.73 billion in sales in 2019, marking its peak. However, with biosimilar competitors already in Europe and expected in the U.S. by 2023, Humira's sales could drop to $6.83 billion by 2026. To manage this impending decline, AbbVie completed a $63 billion merger with Allergan, a strategic move to diversify its portfolio and mitigate the risks associated with Humira's patent cliff. (16)

Other well-known example is Prozac (fluoxetine), a drug developed by Eli Lilly's, which patent expiration in 2001 had great impacts in the company’s earnings. Within 1 year, more than 10 generic companies launched generic fluoxetine, which resulted in revenues decreasing from $1,300 million, in the first half of 2001, to $380 million in the same period of 2002, meaning a total loss in market share and revenues above 70%. (17)

Despite rising R&D costs, the pharmaceutical industry's profitability has remained stable over the past 20 years, consistently generating economic profit compared to other R&D-

intensive sectors. Factors contributing to this stability include the evolution of business models, adoption of open innovation strategies, market expansion, rising drug prices, changes in R&D pipelines, and an increasingly focus on the development of drugs targeting small populations ("targeted" and orphan drugs). The industry's high barriers to entry, its reliance on advanced screening technologies, on licensing agreements with academic institutions, and worldwide collaboration networks in drug development and pre-clinical research also contribute to steady profit margins.

Collaboration has become indispensable in the pharmaceutical industry. As the innovation productivity gap continues to widen, open innovation—focused on fostering relationships with both internal and external stakeholders—has emerged as a key strategy for many large pharmaceutical companies. (18) Emerging biopharmaceutical companies and startups have also become pivotal in boosting productivity across the R&D process, significantly impacting healthcare. (5,19)

In this context, the aims of this master's thesis are:

1. To explore open innovation models in the pharmaceutical industry that enhance collaboration and accelerate R&D;
2. To examine the rise of biotechnology and its synergistic relationship with the pharmaceutical industry;
3. To evaluate the impact of biotechnology on healthcare and identify key success factors that contribute to the sustainability and growth of startups in this sector.

2 Methods

The literature search primarily focused on English-language publications from 2003 to 2024, emphasizing documents published from 2018 onward. Publications prior to 2003 were excluded unless they were recognized as foundational or provided significant contributions to key concepts in the field.

An exploratory, narrative review approach was adopted to capture and synthesize key concepts, historical developments, and recent advancements in Open Innovation Models and Biotechnology. Given the scope and evolving nature of these topics, the literature review followed a flexible and iterative process, allowing for a comprehensive examination of relevant themes without a hypothesis-driven focus. This adaptive strategy enabled the research to refine its focus as new insights emerged, promoting a thorough exploration across interconnected themes.

The search strategy included primarily peer-reviewed journal articles and book chapters, with reports, web articles and news included only from credible sources that offered meaningful contributions to current industry history, practices, and trends. To ensure comprehensive coverage and for key documents, the snowball search method was employed, tracing citations to uncover additional relevant literature.

Bibliographic data was sourced from multiple databases and platforms, including Google Scholar, ResearchGate, ScienceDirect, Springer, SAGE, Scopus, Elsevier, MDPI, Emerald Insight, EMBO Reports, Embase, Cambridge University Press, and Oxford Academic. Key journals consulted included the International Journal of Entrepreneurship and Small Business, International Entrepreneurship and Management Journal, International Journal of Entrepreneurial Behaviour and Research, Strategic Entrepreneurship Journal, Journal of Pharmaceutical Innovation, Journal of Open Innovation: Technology, Market, and Complexity, International Journal of Environmental Research and Public Health, Foundations and Trends in Entrepreneurship, European Journal of Innovation Management, Drug Discovery Today, and Nature Biotechnology. Furthermore, relevant reports and key information were sourced directly from stakeholders' web pages.

Keywords used in the search included "Pharmaceutical Industry," "Biotechnology," "Open Innovation," "Healthcare" and "Startups". Boolean search techniques and synonym-based keyword expansion were employed to ensure a comprehensive literature sample.

3 Open Innovation Models

For several decades, pharmaceutical R&D operated within a completely integrated process based on a closed innovation framework, where businesses controlled and executed nearly all operations in the value chain. (19) Even today, large pharmaceutical companies still prime this traditional model, mostly to safeguard IP and clinical trials data from competitors, who would use this knowledge to enter the market early. (20,21) However, this strategy is no longer sustainable for tackling new challenges, boosting productivity in R&D, and bringing down drug development expenses below the $1 billion barrier. (22)

Increased openness has been presented as a possible solution to the pharmaceutical industry's productivity and efficiency crisis. (23) The concept of 'open innovation,' introduced by Henry Chesbrough in 2003, emphasized leveraging a network of contributors rather than relying solely on internal innovation. (24) Later, in 2006, Chesbrough argued that high-tech businesses, including pharmaceuticals, must adopt open innovation to thrive, since this approach, which harnesses both external and internal ideas to create value, accelerates internal innovation while opening new market opportunities through the free flow of information and knowledge. (25) With this in mind, large biopharmaceutical organizations are increasingly filling scientific and technology gaps through external innovation, combining both traditional and new strategies to develop more effective R&D models. (20)

After assessing the prevailing open innovation processes implemented by twenty-one leading research-based pharmaceutical companies, Schuhmacher (2022) identified 13 commonly used models. These ranged from traditional approaches such as M&A, licensing of IP, R&D collaborations, and joint ventures focused on co-development, to emerging models like corporate venture funds, incubators, public-private partnerships (PPP), crowdsourcing, open-source initiatives, and virtual R&D. (19,26)

Building upon these findings, Iazzolino and Bozzo (2023) propose two distinct groups of R&D partnerships based on the origin of the outsourcing resources, each one having its particular challenges. The first type involves outsourcing products at various stages of the R&D process or even entire processes through open innovation tools like license agreements or M&A. This approach provides immediate benefits, including rapid increase in drug candidates. However, it often comes with higher costs and greater risks. Additionally, an overreliance on direct outsourcing can undermine a company's internal innovation capabilities. In contrast, the second type emphasises outsourcing knowledge by integrating external expertise through

collaborations, partnerships, and open knowledge platforms, and even though, initially, this approach can be challenging due to the complexity of merging internal and external knowledge, it has the potential to yield long-term benefits at significantly lower costs. (27)

To further explore this topic, the following chapters will delve into several open innovation models from the perspective of large pharmaceutical companies, with a particular emphasis on those that involve interactions with the biotechnology sector and startups. By the end of the chapter, the role and contributions of the biotechnology sector and startups to pharmaceutical innovation will become clearer, highlighting the existing symbiotic relationship, which will be further explored in Chapter 4.

3.1 Outsourcing

According to the American Society of Health-System Pharmacists Foundation, outsourcing involves formal agreements between healthcare organizations and external companies to obtain specialized pharmaceutical services or manage pharmacy operations. By leveraging the expertise, technology, and resources of external partners, organisations can improve their operational efficiency and capabilities. (28) This open innovation strategy has emerged as a critical strategy in the pharmaceutical and biotechnology industries. The latter can outsource research services for new drugs or medical devices, avoiding the high costs these processes require if carried out internally and making it possible to proceed to late-stage development and market independently from large pharmaceutical companies. (27)

These external partners can range from small companies to large multinationals, being key providers in the service sector, each focusing on a particular stage of the R&D chain. These can be grouped into three main types: Contract Research Organizations (CRO), which assist in various stages of drug development, from discovery to clinical trials; Contract Development Organizations, which engage in preclinical stages to clinical development; and Contract Development and Manufacturing Organizations/Contract Manufacturing Organizations (CDMO/CMO), which handle tasks from preclinical development all the way to the drug launch and beyond. (29)

Since the early 1990s, outsourcing in pharmaceutical R&D has accelerated significantly, leading pharmaceutical and biotechnology companies to co-discover and co-develop new therapies with technology and services providers, instead of only establishing multiyear contracts. Initially, these alliances focused on early-stage projects but from 2000

onwards the share of mid- and late-stage agreements grew, consequently contributing to a decline in the in-house product development among the larger companies. This trend continued over the past decade, with the outsourcing of both discovery and clinical trials conducted by CRO showing rapid growth. (30)

The global drug discovery outsourcing market is projected for substantial growth, with revenues increasing from $3.5 billion in 2022 to an anticipated $6.3 billion by 2030, representing a compound annual growth rate (CAGR) of 7.4%. In 2022, the lead identification and candidate optimization segment alone generated $1,153 million in revenue, with the U.S. and Europe accounting for 28.3% and 25.8% of global market revenue, respectively. CRO are positioned to benefit significantly from this trend, as 75% to 80% of biopharmaceutical R&D spending can be outsourced. (31) One example is Syngene International Ltd., a CRO, which, in 2018, extended its partnership with GlaxoSmithKline (GSK) to identify new drug candidates with the potential to address some of the world's most pressing healthcare needs. (32) Since 1998, this CRO has partnered with Bristol Myers Squibb (BMS), implementing the Biocon BMS R&D centre in 2007, which supports BMS in developing medical products. This collaboration not only gave place to the development of 10 drug candidates but also reduced the time and costs associated with advancing new compounds. Another example is Syngene Amgen R&D Centre which focuses on multi-disciplinary drug discovery and development. Here scientists collaborate with Amgen’s global R&D teams in projects covering areas such as bioanalytical research, biologics, bioprocess, drug metabolism, medicinal and process chemistry, pharmacokinetics, and pharmaceutical development. (33)

Pharmaceutical companies adopt different outsourcing strategies based on their size. Large companies tend to outsource for strategic reasons, such as improving process development or managing clinical trial supplies, often to prevent bottlenecks or resource shortages. Mid-sized companies focus on one or two products from their own R&D, outsourcing advanced intermediate products rather than older compounds. Startups, lacking the internal resources for development and production, rely heavily on outsourcing, often making them a key market for pharmaceutical service providers. (19)

Chemistry and biology services are the two main segments of the drug discovery outsourcing industry. Due to the growing need for high-quality drug chemical synthesis services and the substantial number of small molecules outsourcing projects, particularly from smaller pharmaceutical companies, the chemistry industry is leading. Biology services are predicted to grow the fastest between 2023 and 2030, at a 7.5% annual rate, attributed to the demand for

technical competence in regulatory compliance and drug discovery. Two examples of leading suppliers of CRO/CDMO services are Aurigene Pharmaceutical Services Ltd., and Eurofins, which achieved the CRO Leadership Award for seven consecutive years. (34,35)

In 2022, small molecule pharmaceuticals accounted for over 77.7% of the drug discovery outsourcing market, particularly in the development of treatments for oncology, cardiovascular, autoimmune, and respiratory diseases. This segment is projected to grow at the fastest rate during the forecast period due to its effectiveness, cost advantages, and ability to target intracellular sites. The increased focus on cancer research and ongoing studies to develop new therapeutics are expected to further drive growth in this segment. (31)

3.2 Strategic R&D Collaborations

Collaborations, partnerships and alliances represent the most standardised open innovation model in the pharmaceutical sector, often involving academic institutions and biotechnology companies. (26,27) These partnerships allow pharmaceutical companies to engage in university-industry collaboration (UIC) R&D projects, gaining access to innovative research, resources, and expertise in various technology fields and therapeutic areas. (36) By collaborating with academic institutions, pharmaceutical companies can also form strategic alliances that facilitate drug licensing and commercialization. (37) Naturally, these partnerships also benefit the academic and biotechnology partners, by providing access to additional technical expertise and resources without requiring them to look for a strategic investor or run the risk of losing control over their drug candidate. (19)

Specific data on UICs in R&D projects within the pharmaceutical sector is limited. However, notable examples of successful partnerships do exist. One such collaboration is between GSK and the Division of Signal Transduction Therapy at the University of Dundee, which led to the development of Dabrafenib (Tafinlar), an anti-cancer drug targeting melanoma. (38). Another example is the partnership between Novartis International AG and the University of Basel, which resulted in the founding of the Friedrich Miescher Institute for Biomedical Research (FMI) in 1970. Approximately 70% of FMI's funding is provided by the Novartis Research Foundation, and the institute's students and scientists actively participate in teaching and research at the University of Basel. This collaboration has been highly productive, with 90% of the 191 papers published between 2012 and 2016 being featured in the Nature Index. (39)

To strengthen UIC, several pharmaceutical companies have reallocated their R&D centres near top universities. Pfizer, for example, in 2014, established a research centre in Cambridge, Massachusetts, home to the Massachusetts Institute of Technology (MIT) and Harvard University, two of the most prestigious academic institutions in the world. Pfizer operated its global headquarters for the Centre for Therapeutic Innovation (CTI) in Massachusetts. CTI, with additional locations in New York City, San Diego, and San Francisco collaborates with leading academic medical centres in these key innovation hubs. (40)

Research done by John Qi Dong in 2019 suggests that companies aiming to develop breakthrough innovations are more likely to do so by including universities in their portfolios. (41) However, despite the pivotal contributions of academia in discovering new drugs, pharmaceutical companies seldom promote the academic origins of their drugs. This lack of recognition makes it difficult to trace whether a new molecular entity originated from academic research, resulting in the underappreciation of these sources. (42)

Additionally, balancing early result publication with IP protection is a constant challenge. Academia prioritizes the dissemination of knowledge through timely and promptly shared publications with the scientific community, while companies need to secure IP barriers to maintain their competitive edge. This dynamic requires clear agreements on IP ownership. (17) Additionally, cultural differences between academia's focus on basic research and the industry's emphasis on product development require effective communication. Aligning these differing objectives can be challenging, as academic goals do not always align with commercial interests. Furthermore, navigating the complex regulatory landscape together demands coordination. (43) Despite these challenges, most parties recognize the competitive nature of the industry and typically agree to reasonable publication delays for patent filing, ensuring all parties receive a fair ROI and contributions. (17)

3.3 Mergers And Acquisitions

Mergers and Acquisitions (M&A) represent traditional open innovation strategies that continue to be popular in the pharmaceutical industry. These are among the primary ways

companies change their structure, scope[2] and scale[3]. (26,44) While often used interchangeably, "merger" and "acquisition" have distinct meanings. A merger involves two companies of similar size joining forces to create a single entity, whereas an acquisition occurs when a larger company takes over a smaller one, fully integrating it into its operations. (27)

Also, M&A transactions fall into two main categories: mega-mergers, where large companies merge with or acquire other major entities, and bolt-on acquisitions, where a large company buys smaller or mid-sized companies, often in the biotech sector, to expand its operations. (45) Organizations can implement a mix of aggressive and defensive strategies to outpace competitors and secure long-term growth. For example, acquiring early movers in emerging technologies can rapidly boost sales, enhance capabilities, and reduce competition, helping to solidify a company's standing in the industry. (42)

Typically, M&A strategies are generally employed once clinical proof of concept is demonstrated, usually after phase I or during phase II trials. The goal is to boost innovation output and, consequently, improve ROI. (29,46) These strategies provide companies with opportunities to enhance their market presence, fill R&D pipelines with new products, and acquire patented technologies of strategic importance. Additionally, M&A can reduce costs through synergies in infrastructures, administration, sales, taxes, and R&D, while offsetting revenue losses from expiring blockbuster drug patents and the rise of generic competition.

Pharmaceutical companies often work to ensure the smooth operation of international sales divisions of newly acquired companies, which helps strengthen distribution channels, maintaining, or even increasing, revenue from global markets. (47)

In 2023, the value of M&A transactions in the biotechnology and pharmaceutical sector reached approximately $280 billion. (48) Major companies performed notable deals included Pfizer’s purchase of Seagen for approximately $43 billion, driven by Seagen's advanced antibody-drug conjugate (ADC) technology and its portfolio of oncology drugs, which is projected to add $10 billion to Pfizer’s revenues by 2030. AstraZeneca's $39 billion acquisition of Alexion Pharmaceuticals to strengthen its rare diseases segment. BMS acquisition of Karuna Therapeutics for $14 billion to obtain its innovative drug KarXT (xanomeline-trospium), a potential new treatment for schizophrenia targeting M1/M4 muscarinic receptors. Merck & Co.

[2] Economies of scope: “resulting from the use of processes within a single operating unit to produce or distribute more than one product”, also termed “economies of joint production or distribution” (145)
[3] Economies of scale: “when the increased size of a single operating unit producing or distributing a single product reduces the unit cost of production or distribution” (145)

investment of $10.8 billion to acquire Prometheus Biosciences, gaining access to its investigational monoclonal antibody (mAb) PRA023, which targets tumour necrosis factor-like ligand 1A (TL1A), holding promise for treating intestinal inflammation and fibrosis. AbbVie's $10.1 billion purchase of ImmunoGen provides access to the marketed drug ELAHERE (mirvetuximab soravtansine-gynx) for ovarian cancer and a pipeline of follow-on ADC. Sanofi's $2.9 billion purchase of Kadmon Holdings to expand its transplant and autoimmune drug portfolio. And, more recently, in 2024, Johnson & Johnson's acquisition of Ambryx Biopharma for $2 billion, is expected to accelerate the development of the company's Phase I/II ADC targeting metastatic castration-resistant prostate cancer. (49)

While M&A can drive financial gains, they do not always contribute to the intended outcomes and may even be counterproductive. (50) A study by Melanie Büssgen (2022) analysed M&A among the top 30 pharmaceutical companies to assess their impact on corporate success. The study found that even though M&A positively influenced revenue, employee count, gross profit, net profit, and return on assets, they did not significantly affect market share, R&D spending, product launches, pipeline size, earnings before interest, taxes, depreciation, and amortization, share prices, or market capitalization. (44) M&A and alliances are inherently complex processes, marked with a high degree of uncertainty, with significant investments of time and resources that do not always result in measurable ROI. In fact, studies suggest that up to 21% of innovation-based acquisitions are said to succeed, while 79% fail. (51)

These results underscore the importance of thorough planning and execution of M&A operations. While such transactions promptly improve financial indicators, in order to guarantee long-term success, it is required careful attention to transaction risks, accurate valuations, effective integration, and value management. (50)

Interestingly, corporate divestitures have emerged as a strategy to unlock pharmaceutical innovation within the pharmaceutical sector. (46) Emilie R. Feldman (2016) defined divestitures as "the removal of one or more of a company's lines of business via selloff or spin-off [4]. (52) More recently Killian J. McCarthy (2024), expanded on this definition by describing corporate divestitures as "the disposal and sale of the assets, facilities, product lines,

[4] A spin-off occurs when a parent company creates a separate, independent entity by distributing shares of an existing division or business to its shareholders. This new company typically operates under a different name and management, though it may still receive some financial or technological support from the original parent organization. Spin-offs are often pursued when the parent company believes that the new, independent entity will have greater value on its own than it did as part of the larger company. (146)

subsidiaries, divisions, and business units of a company." (46) For example, on October 4, 2023, Novartis completed the 100% spin-off of Sandoz, a leader in generic pharmaceuticals and biosimilars, creating a separate, publicly traded company, valued at approximately $11.4 billion. (53)

Killian J. McCarthy (2024) suggests that companies that divest of non-core pipelines or lower-performing commercial products enhance their focus and innovation performance by reducing burdens on their absorptive capacity, which is limited. (46,54) This means that companies can only process and apply a finite amount of external information effectively, and going beyond the limits can complicate coordination, potentially leading to ineffective strategies and costly reorganizations. (41) He argues that such divestitures allow companies to manage a more concentrated set of products and technologies more effectively, ultimately improving their ability to recognize, assimilate, and apply new information. (46) In some cases, divestitures can create opportunities for new M&A, as seen with companies like Merck & Co, GSK, and Novartis. For example, after divesting their consumer groups, Merck & Co acquired Prometheus for $10.8 billion in April 2023, GSK purchased Bellus for $2 billion, and Novartis acquired Chinook for $3.2 billion in June 2023. (55)

3.4 In-Licencing

In-licensing remains a key strategy for pharmaceutical and biotechnology companies seeking to enhance their innovation capabilities. Through these deals, pharmaceutical companies (licensees) acquire IP from other entities, often biotech companies (licensors), in exchange for royalties or other benefits. The agreements can be exclusive or non-exclusive, and negotiations often centre on distributing the value between the licensor and licensee. Since licensees typically handle late-stage clinical development and marketing, they assume greater financial risk, which is reflected in their share of the anticipated product value. (27,29)

For licensees, in-licensing is advantageous as it enriches their pipelines with innovative drugs and technologies. (56) Licensors, on the other hand, benefit from access to the resources needed for final development stages, clinical trials, production, and distribution, while sharing risks with well-capitalized pharmaceutical companies. Additionally, licensors secure funding from the licensed IP, which supports further R&D. This mutually beneficial relationship accelerates time-to-market, increases the chances of late-stage projects reaching the market, and

improves ROI. It also allows licensors to expand their portfolio of potential drug candidates without bearing the full risks and costs of extensive R&D. (19,27)

A notable example of in-licensing collaboration dynamics is Zolgensma, a therapy for spinal muscular atrophy caused by mutations in the SMN1 gene. Initially developed by ReGenX, a biopharmaceutical company specializing in platform technologies, Zolgensma was licenced by Avexis, which obtained exclusive global rights after promising Phase 2 study results. Subsequently, Avexis was acquired by Novartis during Phase 3 trials, and the division was named Novartis Gene Therapies in 2020. (29,57)

In 2022, pharmaceutical companies, globally, signed 385 licensing agreements, a 35% decline from the 593 deal's peak in 2020. Despite the reduction, the total value of these agreements remained stable, with a total upfront cash and equity value of $166.4 billion, a minor reduction from the $170.6 billion in 2020. This can be attributed to a focus on high-value deals, even as the overall number of partnerships decreased. A report from DealForma (2023) supports this trend, noting a 36% overall decrease in R&D partnerships and licensing deals from 887 to 585 during the same period (2020-2022). According to KPMG, this downturn in deal volume is largely attributed to tighter capital markets, anticipated drops in biotech valuations, and funding challenges exacerbated by economic uncertainty and the closure of key mid-sized banks. (58,59)

Another key example of high-value deals during this period is AstraZeneca's $6 billion licensing agreement with Daiichi Sankyo in 2020 for the ADC Datopotamab Deruxtecan, which targets TROP2 in patients with advanced or metastatic nonsquamous non-small cell lung cancer. The agreement included an upfront payment of $1 billion, with an additional $5 billion contingent on achieving specific milestones. This follows a similar high-value licensing arrangement with Daiichi Sankyo for Trastuzumab Deruxtecan (ENHERTU) in 2019, an ADC designed for the treatment of breast cancer, advanced NSCLC and HER2-positive advanced gastric cancer or gastroesophageal adenocarcinoma, which underscores AstraZeneca's strategic focus on oncology. (60,61)

Currently, more than 50% of licensing deals involve preclinical drug candidates, reflecting a strategic focus on early-stage in-licensing. (19) However, there is a noticeable shift toward later-stage deals: in 2023, the number of Phase I deals dropped from 84 in 2022 to 51. This trend reflects a strategic preference towards balancing early-stage and later-stage licensing deals. (59)

As in-licensing continues to evolve, contractual arrangements are becoming more sophisticated, often incorporating success premiums, milestone payments, and royalties instead of simple one-time payments. These agreements are now tailored to specific geographical markets and reflect the risk-benefit profile of the collaboration. Given the unpredictable nature of early-stage partnerships, negotiating such agreements has become more complex, significantly impacting the final contract terms. (62)

An example of this complexity is found in Sage Therapeutics' (the licensor) contractual obligations to their licensees, which highlights the real-world dynamics involved when structuring these deals. (63)

"*(2) We have acquired exclusive and non-exclusive rights to use, research, develop and offer for sale certain products and patents under license agreements with Washington University, CyDex Pharmaceuticals, Inc. and two license agreements with The Regents of the University of California. The license agreements obligate us to make payments to the licensors for license fees, milestones, license maintenance fees and royalties. We are obligated to make future remaining milestone payments under these agreements of up to an aggregate of $28.7 million upon achieving certain milestones, related to clinical development, regulatory approvals and sales. For the year ended December 31, 2018, we recorded $1.0 million of research and development expense under these license agreements."*

3.5 Corporate Venture Capital

Collaborations with entrepreneurs and academic institutions are increasingly important in the pharmaceutical industry. (26) Start-ups drive new scientific discoveries and advances, yet they frequently struggle to secure funding, especially in their early stages. Consequently, they highly rely on various forms of external entrepreneurial financial support (64) Given that up to 80% of R&D pipeline projects in large pharmaceutical companies come from external sources, mainly biotech startups, many companies have turned to CVC as a way to address inefficiencies in traditional R&D methods. (19)

In 2022, Amitabh Chandra reported that 60% of venture capital funding is directed towards drug development within the pharmaceutical and biotech sectors. (65) And, over five years, corporate investors have taken part in 41% of the private venture capital-backed biopharma deals in the U.S., EU, and UK. (66) Thus, underscoring the increasing importance of CVC in driving pharmaceutical innovation while supporting early-stage biotech companies that face challenges securing funding independently.

In the same year, according to Alexander Schuhmacher, 15 out of 21 pharmaceutical companies analysed in open innovation models utilized CVC funds. (26) Notable biopharma corporate investors, in 2022, were Eli Lilly, Pfizer Ventures, and Novartis Venture Fund (NVF) with 30, 29, and 23 deals, respectively. (66) Eli Lilly, for instance, added $50 million in 2023 to its $300 million Social Impact Venture Capital Portfolio, which has provided funding for over 50 start-ups in the United States. (67) Pfizer Ventures announced 8 new biotech investments in areas such as oncology and autoimmune diseases, adding to more than 50 drug development programs advancing in clinical trials, with 14 companies of its portfolio raising nearly $1 billion to support their drug development projects. Among these were Crossbow Therapeutics, which focuses on T-cell receptor mimetics for oncology, Mozart Therapeutics, which develops CD8 Tregs for autoimmune disease, Grey Wolf Therapeutics, working on neoantigens for oncology, and Flare Therapeutics Advancing Drug Transcription Factors. To add, together with Bayer, Amgen and Sanofi, Pfizer Ventures helped Recode Therapeutics secure $260 million in funding for its innovative Lipid Nanoparticle formulations thought to enhance delivery to the liver and other targets. (66,68)

Similarly, NVF manages over $750 million in committed capital and continues to invest in more than 40 early-stage biotech companies across North America and Europe. The fund aims to foster innovation and generate superior returns by targeting companies focused on pioneering life science technologies. For instance, Capstan Therapeutics, which launched in 2022, was provided with $165 million in capital to develop in vivo cell reprogramming therapies, and AstronauTx, which focuses on neurodegenerative diseases, recently closing a $61 million Series A round[5]. (67)

CVC funds offer numerous benefits. By facilitating the support of start-up and biotech companies and outsourcing service companies, they enable a risk-managed expansion of R&D activities and access to new technologies and early-stage innovations without the need for significant investment in individual drug candidates and, at the same time, mitigating the risks of early internal research. (19) Additionally, CVC grants investors preferential rights to R&D programs and early data access, enabling them to swiftly decide on licensing promising projects without the burden of daily operational tasks and management. (17) On the other hand, and

[5] Series A funding is the first major round of investment that typically follows seed funding and angel investing. It allows external investors to contribute capital to a growing company in exchange for equity or ownership stakes. This round is part of a sequence of funding events, including Series B and C, which help companies secure the financial resources needed for further growth and expansion. The term "Series A" refers to the specific class of shares issued during this round. (147)

beyond financial features, CVC provides start-ups with expedited market access, technological sponsoring, and enhanced product visibility through marketing, distribution, and research resources. (69)

The CVC market is highly volatile, operating under market-driven cycles shaped by shifting investor priorities and evolving R&D pipeline needs, where despite billions in annual investments, demand in biotech consistently surpasses available funding capacity. (62) This dynamic has led to increased selectivity in CVC investments, a trend seen by Francesco Corea in 2016. Analysis of nearly 400 deals over a decade (2003-2013) revealed a shift toward more risk-averse strategies, with a preference for investing in young, publicly listed biotech companies that are developing moderately risky, early-stage molecules and are horizontally integrated with other biotech companies. (70) The 2023 Annual Biopharma Licensing and Venture Report further supports this, stating that while pharmaceutical companies continue to seek early-stage deals, they now concentrate on de-risked late-stage deals, such as clinical-stage biotech that address more concrete patient solutions. (59)

Building upon the importance of open innovation models for pharmaceutical companies to remain competitive and transform innovation into financially successful products that enhance global health, the next chapter will focus on the rise of the biotechnology industry. It will explore the significant impact of biotech ventures on pharmaceutical innovation and examine the dynamic, symbiotic relationship between them, as well as the startup ecosystem where startup success factors will be briefly explored. Thus, providing a deeper understanding of how biotechnology has reshaped drug development and continues to drive innovation across the medical field.

4 Biotechnology

4.1 Rise and Synergy with the Pharmaceutical Industry

According to OECD, biotechnology encompasses the use of science and technology applied to living organisms, aiming to develop products and services that benefit health, agriculture, and more. (71) Additionally, a biologic product, a subset of biotech products defined by the FDA, include a wide range of items such as "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine applicable to the prevention, treatment, or cure of a disease or condition of human beings. (72)

These definitions underscore biotechnology's broad scope and applications, setting the stage for an industry that, while rooted in science, has evolved over the past 50 years. This evolution has transformed biotechnology into a field marked by substantial capital investment and long development cycles—often spanning 20-30 years. (73) Due to these lengthy cycles, the sector is still considered to be in its early stages, with most companies having completed only about three full cycles. (74) Biotechnology belongs to a highly regulated industry, requiring specialized expertise and often ethical approvals, especially in areas involving human or animal testing. Moreover, IP protection plays a crucial role in securing the competitive edge for companies, and strong collaborations with universities, research institutions, and other biotech companies are essential, as well as funding since the biotech company's life cycle is a continuous and resource-intensive process. (19)

Key breakthroughs, such as recombinant DNA techniques, laid the foundation for biotechnology's subsequent innovation such genomics, proteomics, and bioinformatics, which are driving growth and propelling its further expansion. (56,75) In 1953, James Watson and Francis Crick's discovery of DNA as the genetic code that defines all aspects of living organisms ignited a scientific revolution centred on understanding protein interactions in the human body. Two decades later, the biotechnology sector emerged, pioneering the use of recombinant DNA (rDNA), techniques to reengineer DNA in cells. (76) The late 1970s and early 1980s witnessed the birth of the modern biotech industry, marked by the establishment of Genentech in 1976, a company that pioneered the development of recombinant protein-based drugs and vaccines, known as biologics. Soon after, mAb technology followed, enabling targeted therapies for a range of diseases. (62) In just 5 years, the success of Genentech spurred the rapid growth of biotech startups in the U.S., with notable early companies like Amgen, Biogen, and Chiron becoming successful. (56)

Initially, pharmaceutical companies viewed biotechnology as a supplementary tool for traditional drug discovery and were sceptical about the value of the innovations being brought by this emergent sector especially when it comes to injectable treatments, further diminishing its perceived significance. While established pharmaceutical companies concentrated on areas like medicinal chemistry, physiochemistry, and pharmacology, biotech companies distinguished themselves by pioneering new fields such as cell biology, molecular genetics, protein chemistry, and immunology. (19) Early alliances, such as Biogen's 1978 licensing deal with Schering Plough and Genentech's 1979 agreement with Eli Lilly for human insulin, were marked by modest financial commitments and promises of future royalties, reflecting a cautious approach and an initial undervaluation of biotech's potential.

The sector was propelled by the U.S. Supreme Court landmark decision in the 1980's case Diamond v*ersus* Chakrabarty, which granted patent rights for newly discovered living organisms, securing critical IP protection and attracting essential investment for biotech. (76) Similarly, the Bayh-Dole Act, signed in the same year, accelerated the commercialization of federally funded research by allowing universities and small businesses to patent and market their innovations. This legislation also empowered federal agencies to offer exclusive licenses, creating significant incentives for businesses to adopt academic technologies. (77) From 1996 to 2020, the Bayh-Dole Act has contributed to the establishment of over 17,000 startups and led to the development of more than 200 pharmaceutical drugs and vaccines. (78) From 1980 onward, as depicted in Figure 2, the increasing number of Biologics License Applications (BLA) compared to New Drug Applications (NDA) reflects the growing significance of biotechnology in disrupting traditional drug development.

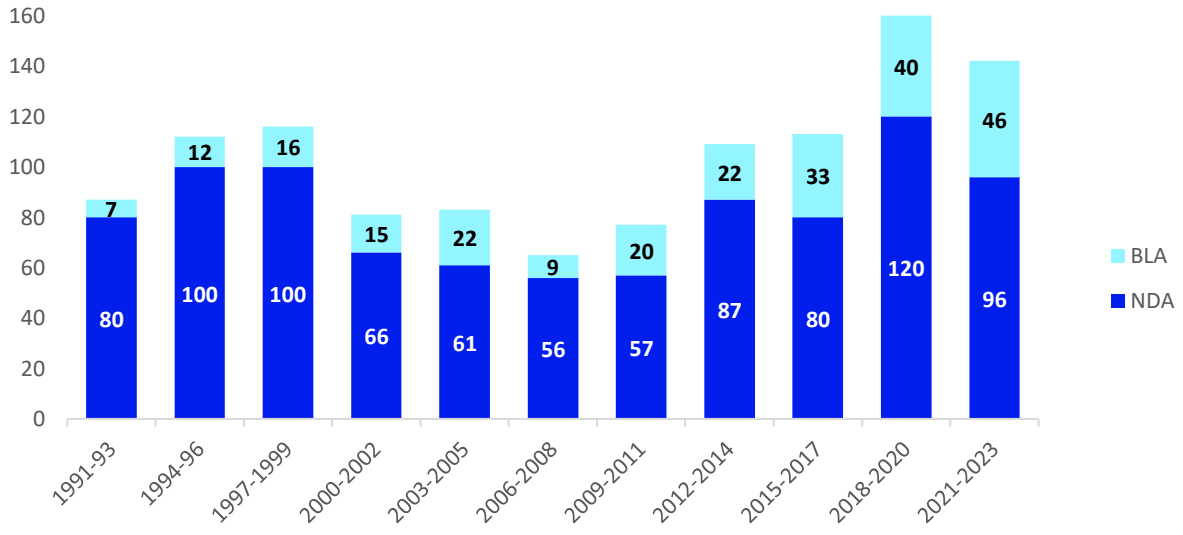

Figure 2. NDA and new biological products approved under a BLA. Source: FDA "Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals."

This prompted pharmaceutical companies to pursue coexistence rather than competition with the biotech sector. (19) By the 1990s, large pharmaceutical companies had started closely monitoring the biotech industry, forming partnerships with startups, and strategically acquiring key players. Early adopters (1990-2001) such as Eli Lilly, Roche, and Novartis recognized biotech's transformative potential and invested heavily in acquisitions, collaborations, and internal research. Eli Lilly in collaboration with Company of Indianapolis, Ind., for example, in 1982, pioneered biotechnology by producing Humulin, the first recombinant DNA-derived drug approved by FDA, under a licence from Genentech. (79)

Roche, for example, acquired a 60% stake in Genentech in 1990, securing exclusive rights to polymerase chain reaction technology in the next year and completing its acquisition in 2008. To add, in 1994, purchased Syntex for $5.1 billion, mostly to expand its product portfolio with innovative drugs under development and strengthen its market position with Syntex's blockbuster drugs like naproxen. (80) Novartis also bolstered its biotech position by creating the NVF, acquiring Chiron, mainly to establish development platforms in the vaccinations and molecular diagnostics markets. (81) These companies' early commitment allowed them to cultivate specialized expertise, integrate external innovations, attract top talent, make strategic acquisitions, and ultimately gain long-term rewards—creating high barriers for latecomers as these early investments valued significantly by the 2000s.

In contrast, companies like Pfizer, BMS, and Sanofi were slower to embrace biotech, initially making smaller investments that focused on partnerships and minor acquisitions. However, they eventually made significant strides, exemplified by Sanofi-Aventis's $20 billion acquisition of Genzyme in 2011, which expanded their rare disease treatments and strengthened their renal-endocrinology, hematology-oncology, and biosurgery divisions. Similarly, Abbott's acquisition of Knoll paved the way for the development of Humira, one of the world's best-selling drugs. (82)

By the early 2010s, these strategic investments began to pay off, as biologic drugs gained FDA approval and became blockbusters. By 2015, six of the top ten best-selling drugs globally were biologics, signalling a clear shift in the industry toward biotech-based treatments. (83) Between 2015 and 2021, biotech R&D was responsible for 47% of new product launches by the top 20 biopharma companies, surpassing internal R&D's contribution of 38%. And, by 2023, biotech's dominance was evident, with biologics accounting for 70% of the top 20 best-selling drugs globally. (84) That year, the FDA approved 80 new biopharma products, matching the highest annual total of the century (paring with 2018 numbers), reflecting a growing regulatory acceptance and highlighting biotech's pivotal role in driving innovation.

The interplay between the two sectors has fostered a highly collaborative environment, often referred to the integrated field of "biopharma" or, more generally, life sciences. This relationship underscores the transformative impact of biologics compared to the traditional focus on small molecules. These collaborations create a win-win dynamic, where pharmaceutical companies leverage biotech's innovative technologies and early-stage research capabilities, and biotech companies benefit from the critical funding, validation, and access to extensive resources from their larger partners, including expertise in manufacturing, regulatory affairs, and marketing. This synergy has been crucial in advancing more precise targeting of diseases and the development of personalized treatments.

Today's value chain in drug development reflects this integrated approach, where both biotech and pharmaceutical companies play distinct but complementary roles, enhancing the overall efficiency of the drug development process. (75,76)

The 6D R&D Framework[6] – Discovery, Development, Design, Deployment, Delivery, Differentiation – outlines the biotech value chain, from identifying genetic targets to market positioning of biopharma products. Through Figure 3 the diverse roles biotechnology companies play across the pharmaceutical R&D process are illustrated. In the Discovery stage, R&D companies focus on innovative activities such as gene identification, concept development, and academic collaborations. The Development stage encompasses clinical and preclinical services, including testing, risk assessment, and regulatory compliance, preparing products for market approval. During Design, agencies provide market analysis, quality control, and prototype development, aligning products with market needs. The Deployment stage involves regulatory compliance and manufacturing, ensuring smooth scale-up and production. In the Delivery phase, companies manage distribution, sales, and marketing to bring the product to consumers. Finally, in the Differentiation stage, companies ensure long-term competitiveness through IP protection, post-marketing surveillance, and strategic market positioning. (85,86)

[6] This framework was created for the all-purpose of explaining the biotech value chain.

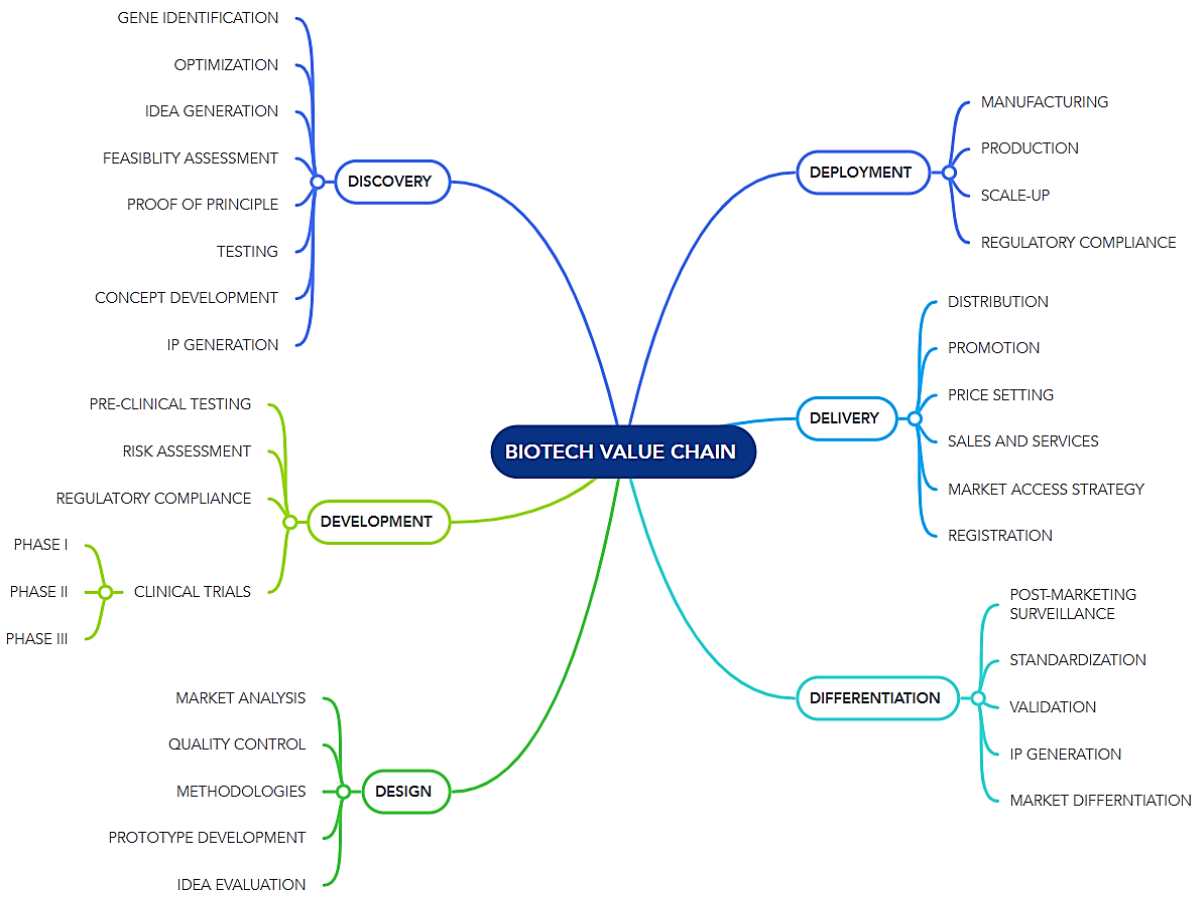

Figure 3. Biotech value chain in the R&D process. Adapted from the Book "Innovation and Entrepreneurship in Biotechnology – An International Perspective"

Before moving to the next chapter, it is essential to highlight the evolution of biotechnology, which can be categorized into three distinct phases as proposed by Dennis Purcell, Founder & Senior Advisor of Aisling Capital. These phases are as follows: Biotech 1.0 (1980-2000), driven by two groundbreaking innovations such as rDNA and monoclonal antibodies (mAb); Biotech 2.0 (2000-early 2020s) shaped by the completion of the Human Genome Project (2001-2003), which generated the first complete sequence of the human genome, laying the foundation to personalized medicine and identifying markers attributed to various diseases; and the current Biotech 3.0 era, where the focus has shifted toward addressing widespread chronic disease such as obesity, Alzheimer, and non-opioid pain management and integrating emerging technologies like artificial intelligence. (87)

In the upcoming chapter, a comprehensive overview of the second and third phases will be provided. This overview will display relevant and innovative technological approaches, therapeutic areas attracting significant investment and clinical trial efforts, and will offer insights into the biotechnology startup ecosystem, highlighting key success factors.

4.2 Impact in Healthcare

Biotechnology has revolutionized the healthcare landscape, and its positive impact is undeniable. At the heart of the biotech sector are key characteristics that drive this innovation. These include a focus on groundbreaking technologies, a deep reliance on scientific discoveries to advance product development, and the dedication in addressing unmet medical needs by creating novel biologic treatments. (75) As a result of these efforts, life expectancy has increased, and the rates of mortality and disability associated with various diseases have decreased. This progress benefits society at large, allowing individuals to live healthier lives. Furthermore, the proliferation of new drugs and advanced technologies has broadened access to treatments, diversified the drug market, and, in some cases, reshaped the pricing paradigm for drugs. (76)

Biopharmaceuticals gave place to a new era in medicine, where complex biological molecules can be engineered to create treatments tailored to an individual's genetic profile. (88) In the healthcare sector, biopharmaceuticals are driving innovation throughout the "Diagnosis-Prevention-Treatment" spectrum. Biotech companies are introducing both follow-on (FO)[7] drugs, often referred to as "me-too" drugs, and first-in-class (FIC) [8] drugs to treat a wide range of diseases. (89)

For instance, a noteworthy FO drug is Repatha (Evolocumab), developed by Amgen, which is an LDL-cholesterol (LDL-C) lowering mAb. Approved by the FDA in August 2015, Repatha was released just one month after Praluent (Alirocumab), a FIC drug developed by Regeneron and Sanofi, which also belongs to the proprotein convertase subtilisin kexin type 9 - PCSK9 - inhibitor class. Both drugs are approved for adults with hypercholesterolaemia, including heterozygous familial and non-familial, as well as mixed dyslipidaemia, However, Repatha is also approved in pediatric patients aged 10 years and older with homozygous familial hypercholesterolaemia. Moreover, Repatha is available in three different pharmaceutical forms, offering more options than Praluent, which comes in only one formulation. (90,91)

Biotechnology's impact extends to preventive medicine, particularly through vaccine development, as seen during the Covid-19 pandemic. Emerging biotechnology startups,

[7] Follow-on (FO) therapies are new medications authorised within an established therapeutic class that provide incremental therapy improvements, more options for physicians and patients, and possible pricing competition. (148)

[8] First-in-class (FIC) medications introduce unique mechanisms of action and extend therapy choices for patients by targeting molecules not previously targeted. (149)

Moderna Therapeutics, with Spikevax, and BioNTech, which partnered with Pfizer to develop Comirnaty, harnessed the power of mRNA technology to deliver solutions in record time, effectively addressing this global challenge. (92,93) According to the World Health Organisation, more than 1.4 million lives have been saved in the European Region as a result of COVID-19 vaccination, which has reduced deaths by at least 57%, especially among the most vulnerable populations aged 60 or older. (94,95)

A significant advancement in preventive medicine is the development of human papillomavirus (HPV) vaccines Gardasil and Gardasil 9, introduced by Merk & Co in 2006 and 2014, respectively. HPV is a sexually transmitted infection that spreads through skin-to-skin or skin-to-mucosa contact and is linked to cervical and anal cancer, genital warts as well as head and neck squamous cell carcinoma (HNSCC). Gardasil 9 was developed to offer protection against HPV6, 11, 16, 18, 31, 33, 45, 53, and 58 - covering five additional virus-like particle types than the original Gardasil, This expansion increases cervical cancer protection rates from 70%-75% to approximately 90%, for example. (96) These developments have been reshaping the landscape of vaccine development, proving the potential, adaptability and resilience of biopharmaceuticals in both treating and preventing diseases. (93)

Another example is the field of Proteomics[9], which became an essential part of drug development and has significantly enhanced biopharmaceutical efforts in disease biomarker discovery for diagnostics. (97) Between 2000 and 2018, the use of biomarkers in oncology clinical trials increased from 5% to 55%, with prostate cancer (86%), melanoma (74%), and breast cancer (69%), leading the way. Currently, a wide range of biomarkers including HER2, EGFR, KRAS, BRCA1/2, and PD-1/PD-L1, are intricately linked to therapeutic strategies for various cancers, such as breast cancer, non-small cell lung cancer, and ovarian cancer. (98)

Recent advancements have also highlighted a growing focus on pan-tumour biomarkers, including vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF). These factors are critical regulators of angiogenesis and tumour growth. VEGF plays a pivotal role in promoting blood vessel formation, while FGF engages in essential cellular processes, such as proliferation and survival. Both have emerged as vital prognostic indicators and

[9] Proteomics is a scientific discipline focused on understanding proteins, their abundance, variations, and modifications, as well as their interactions and networks that regulate cellular processes. It involves both small- and large-scale studies, ranging from characterizing a single protein to identifying and measuring thousands of proteins that together shape cellular function. (150)

therapeutic targets, with their levels correlating with tumour aggressiveness and treatment response, underscoring the potential of these biomarkers in guiding personalized treatment approaches in oncology.

Additional information on this topic can be found in an in-depth review by Yue Zhou (2024), which explores tumour biomarkers for diagnosis, prognosis and targeted therapy. (99)

4.2.1 Innovative Therapeutic Approaches

The biopharmaceutical sector has ushered in a transformative era, characterized by innovative approaches to clinical development for complex medical conditions. Some of these innovative approaches have already shown their worth through successful and tangible applications, while other emerging therapies are anticipated to pave the way for future breakthroughs. (89) Table 1 highlights key biotechnological approaches, including recent biologics introduced by startups and already approved by the FDA. (88)

Among the most significant breakthroughs in biotechnology is the development of clustered regularly interspaced short palindromic repeats (CRISPR) technology, specifically the CRISPR-associated protein 9 (Cas9). (93) As a third-generation gene-editing tool, CRISPR-Cas9 is more cost-effective and efficient than its predecessors, zinc-finger nucleases, and transcription activator-like effector nucleases. This technology employs guide RNA to direct Cas proteins to precise locations within the genome, making it a versatile tool for treating genetic disorders such as haemophilia, sickle cell disease (SCD), and beta-thalassemia. Its potential to advance drug development lies in its ability to identify new therapeutic targets and facilitate the screening of novel therapies, including CAR-T immunotherapy and base editing. (100,101) A notable achievement is the FDA's approval in 2023 of CASGEVY (exagamglogene autotemcel), an autologous genome-edited hematopoietic stem cell therapy developed by Vertex and CRISPR Therapeutics, designed to treat SCD in patients aged 12 and older who experience recurrent vaso-occlusive crises. (102,103)

Although RNA and oncolytic virus's (OV) base therapies have yet to receive the FDA approval in 2023-2024, both fields are progressing rapidly. As of April 2024, 21 RNA-based therapies have been approved, which include 10 ASOs, 6 siRNAs (primarily targeting neurological conditions, cardiovascular diseases, and metabolic disorders) as well as 5 mRNA vaccines, so far limited to those developed for COVID-19. According to Avalere's 2024 report, approximately 131 unique RNA-based therapies are in clinical development, predominantly in

early-stage development (Phase I and II). Notably, over one-third (37%) of these therapies focus on rare diseases, while 21% target conditions with fewer than two approved disease-modifying therapies (DMTs), highlighting their potential to introduce novel treatments options. (104)

OV have also secured a role as powerful agents in cancer therapy, particularly when used in combination strategies. This field has seen significant milestones, starting with the approval of RIGVIR (SND005) in Latvia in 2004, marking the first oncolytic drug for melanoma. In 2006, China approved ONCORINE (H101) for HNSCC, followed by IMLYGIC (Talimogene laherparepvec, T-VEC) for the treatment of recurrent melanoma in 2015, FDA's first OV approval. More recently, in 2020, China approved DELYTACT (teserpaturev/G47Δ) for malignant glioma, which demonstrated promising survival benefits and a good safety profile, representing a significant step forward in brain cancer treatment. (105,106)

FIC drugs represent a major breakthrough in medical innovation by introducing unique therapeutic mechanisms that set them apart from existing treatments. In 2023, 69 new NAS were launched worldwide, contributing to a five-year total (2019-2023) of 362, with 42% of these classified as FIC. This trend highlights their importance within the biopharmaceutical pipeline, especially in oncology and neurology, which together accounted for 56% of launches. Notably, nearly half of the new drugs were biologics, with several groundbreaking cell and gene therapies, including, OMIDUBICEL (Omisirge), the first allogeneic pancreatic islet cellular therapy for Type 1 diabetes; ROCTAVIAN (Valoctocogene roxaparvovec), a revolutionary gene therapy for hemophilia A, and Arexvy, the first vaccine for respiratory syncytial virus. With projections of 65–75 new active substances expected to launch annually over the next five years, the landscape for innovative therapies continues to expand. (107)

Table 1. Overview of innovative clinical development approaches

Approach	Definition/Mechanism	Categories	Product / Pharmacologic Class	Year of Approval	Company	Indication(s)	Ref.
Gene-Modified Cell Therapy	Technique that involves extracting specific cells from a patient, genetically modifying them outside the body, and reintroducing them to enhance the patient's ability to fight a disease.	CAR T-cell, TCR, TILs NK, MILs Dendritic cells	LENMELDY (atidarsagene autotemcel) HSC gene therapy	2024	Orchard Therapeutics Limited	Treatment of children with PSLI, PSEJ or ESEJ - MLD.	(108) (109)
Gene Therapy	Technique that uses genes to treat, prevent, or cure diseases by either adding new copies of a faulty gene or replacing a defective or missing gene with a healthy version.	Plasmid DNA Viral vectors Bacterial vectors	ELEVIDYS (delandistrogene moxeparvovec-rokl) AAV vector-based gene therapy	2023	Sarepta Therapeutics, Inc.	Treatment of ambulatory patients aged 4. through 5 years with DMD with a confirmed mutation in the DMD gene	(110) (111) (112)
Cell Therapy	Technique that treats diseases by restoring or modifying specific cells or using them to deliver therapies. This involves cultivating or altering cells outside the body before transplanting them into the patient. Cells may be sourced from the patient (autologous) or a donor (allogeneic). and can be categorized into undifferentiated stem cell therapy and fully differentiated cell therapy.	Undifferentiated stem cell therapy Fully differentiated cell therapy	LANTIDRA (donislecel) [2] Human allogeneic cellular suspension	2023	CellTrans Inc.	Treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycaemia despite intensive diabetes management and education	(113) (114) (115)
RNA Therapy	Technique that uses non-replicating nucleic acids to modify disease pathways. RNAi and antisense reduce or eliminate the production of an unwanted protein. mRNA products are intended to trigger the synthesis of a novel therapeutic protein.	RNAi (siRNA), ncRNAs (subclass: circRNA), ASO mRNA, Aptamers	OXLUMO (lumasiran) HAO1-directed siRNA	2020	Alnylam Pharmaceuticals	Treatment of PH1 to lower urinary oxalate levels in paediatric and adult patients	(104) (116) (117)
Oncolytic Virotherapy	Technique that uses viruses to selectively target and destroy cancer cells while sparing normal ones, oncolytic virotherapy can transform "cold" tumours[1] into "hot" by modulating the tumour microenvironment. OVs reduce immunosuppressive cells (Tregs, MDSCs) and cytokines (IL-10, TGF-β) while boosting proinflammatory cytokines (IL-6, IL-8) and attracting immune cells like NK cells. This process enhances tumour antigen release, promotes immunogenic cell death, and activates CD8+ T cells, which can attack both injected and distant tumours, amplifying the anti-tumour immune response.	dsDNA viruses (herpesvirus, vaccinia virus, adenovirus etc.,) ssRNA viruses: Positive-sense (poliovirus, Seneca Valley virus, coxsackievirus), AND Negative-sense (Newcastle Disease virus, measles virus, vesicular stomatitis virus);	IMLYGIC (talimogene laherparepvec) Attenuated HSV-1 encoding GM-CSF	2015	Amgen	Treatment of genetically modified oncolytic viral therapy is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma that recurs after initial surgery.	(118) (105) (119)

Aptamers: RNA molecules that bind proteins or other ligands (still an emerging technology); ASO: Antisense Oligonucleotide (inhibits mRNA translation); AVV: Adeno-associated virus; CAR T-cell: Chimeric Antigen Receptor T-cell; circRNA: Circular RNA-based vaccine; DMD: Duchenne muscular Dystrophy; ESEJ: Early Symptomatic Early; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HAO1: Hydroxy acid Oxidase 1; HSC: Autologous Hematopoietic Stem Cell; HSV-1: Herpes Simplex Virus Type 1; MLD: Juvenile Metachromatic Leukodystrophy; MILs: Marrow-derived Lymphocytes; mRNA: Messenger Ribonucleic Acid (facilitates protein synthesis); ncRNAs: Non-coding RNA; NK: Natural Killer cells; OV: Oncolytic Viruses; PH1: Primary Hyperoxaluria Type 1; PSLI: Pre-symptomatic Late Infantile; PSEJ: Pre-symptomatic Early Juvenile; RNAi: RNA interference therapy (blocks mRNA translation); siRNA: small interfering RNAs; TCR: T-cell receptor; TILs: Tumour-Infiltrating Lymphocytes

[1] Cold tumour are tumours that lack tumour antigens, have few T cells recognizing those antigens, and contain high levels of immunosuppressive cells (Tregs, MDSCs, M2 macrophages) and cytokines (IL-10, TGF-β), making them resistant to immune checkpoint inhibitors (ICIs); [2] Purified allogeneic islets of Langerhans for transplant;

4.2.2 Advancements in Oncology and Neurology

Recent advancements in scientific research are driving a shift toward innovative therapeutic models with approaches such as gene and cell therapies, ADC, and multi-specific antibodies at the forefront. These innovative approaches now account for approximately 25% of ongoing oncology trials, for example, and are being applied to rare disorders, which constitute 70% of trials in this category.

According to the *IQVIA Global Trends in R&D 2024* study, oncology and neurology are leading therapeutic areas in both trial volume and investment, representing over 54% of the total drug development pipeline. In 2023 alone, these two fields accounted for a significant portion of the 4,873 planned or initiated studies across Phases I to III, with oncology alone constituting 44% of this pipeline. (107)

Research in neurology continues to focus on treating neurodegenerative, neuromuscular, and psychiatric conditions, particularly Parkinson's and AD, where the development pipeline includes disease-modifying treatments that slow or halt the progression of diseases, rather than merely alleviating symptoms. Similarly to oncology, there has been a gradual exploration of advanced biotherapeutics, such as cell and gene therapies for neurological conditions, which have made up 5% of the pipeline over the past five years. (89)

The substantial research activity towards oncology and neurology are further evidenced by the number of high-value deals exceeding $2 billion that took place in 2023. Oncology led the field with 12 deals, totalling $109.68 billion, of which six were ADC-related, followed closely with 4 deals in neurology valued at $34 billion. (107) Within the startup ecosystem, recognised for driving innovation, DealForma reported a robust VC investment in seed and Series A rounds in 2023. Investments in biologics, antibodies, DNA and RNA therapies, cell therapy and vectors, as well as gene editing technologies like CRISPR, collectively attracted $3.522 billion, compared to $1.248 billion in small molecule investments. Specifically, investment was heavily concentrated in cancer and neurology, which received $1389 million and $639 million, further validating the sector’s strategic prioritisation of these therapeutic areas. (59)

AbbVie, a leading biopharmaceutical company, has shown high interest in oncology, recently performing the acquisition of ImmunoGen for $10.1 billion, which was announced in November 2023. This acquisition strengthened AbbVie’s ADC pipeline and included ImmunoGen’s flagship cancer therapy ELAHERE (mirvetuximab soravtansine-gynx), a FIC

ADC targeting folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate. (120) ELAHERE is indicated for the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. (121) Following promising clinical results, ELAHERE received accelerated approval from FDA in 2022, achieving full approval in March 2024, after the completion of a large Phase 3 MIRASOL trial (NCT04209855), designed by the FDA. (122)

In March 2024, AbbVie completed the acquisition of Cerevel Therapeutics for $8.7 billion, thereby enhancing its neuroscience pipeline with Cerevel's promising clinical-stage assets targeting neurological and psychiatric conditions. This acquisition granted AbbVie access to Tavapadon, a FIC selective partial agonist for dopamine D1/D5 receptors to the treatment of Parkinson's disease. As a once-daily oral medication, Tavapadon is being studied as both a standalone treatment and as an adjunct therapy to levodopa, to deliver effective symptom management for patients in the early stages of the disease. (120) AbbVie's TEMPO clinical development program encompasses key trials evaluating Tavapadon in various dosing regimens. TEMPO-1 (NCT04201093) and TEMPO-2 (NCT04223193) focus on evaluating fixed doses (5 and 15 mg QD), and flexible doses (5-15 mg QD) of Tavapadon as standalone therapies for early-stage PD. In addition, TEMPO-3 (NCT04542499) explores the effectiveness of flexible-dose Tavapadon (5-15 mg QD) when used alongside levodopa. Participants who finish these studies may also have the opportunity to enter the open-label TEMPO-4 trial (NCT04760769), which aims to investigate the long-term safety and efficacy of Tavapadon. (123) In September, AbbVie announced positive results from the Phase 3 TEMPO-1 trial, validating the drug's potential. (124)

The increasing focus on neurological disorders, particularly AD, aligns with AbbVie's strategic direction. Alzheimer's disease is currently the most common form of dementia, accounting for 60-70% of cases and ranked as the seventh leading cause of death. This progressive neurodegenerative disorder is characterized by significant pathological changes in brain regions responsible for cognitive function, while also impacting personality and behaviour. Today, over 55 million people worldwide are living with dementia, with more than 60% of these cases found in low- and middle-income countries. Each year, nearly 10 million new cases are diagnosed, which means that every 3.2 seconds one new case is discovered. In 2019, the economic burden of dementia reached a staggering $1.3 trillion, with about half of these costs stemming from care provided by informal caregivers, such as family members and

friends. Moreover, dementia disproportionately impacts women, who experience higher rates of disability and mortality associated with the disease. (125)

In 2023, AD treatment achieved significant milestones with the FDA's approval of LEQEMBI (lecanemab-irmb) 100 mg/mL injection for intravenous use. LEQEMBI, a humanized immunoglobulin gamma 1 (IgG1) mAb targeting aggregated soluble and insoluble forms of amyloid beta (Aβ), was first granted accelerated approval by the FDA in January based on Phase 2b data showing its efficacy to reduce Aβ plaques in the brain, which is a defining pathophysiological feature of AD. (126) (127) Later, in July 2023, following the results of Study 301 (Clarity AD - NCT03887455), a complementary Phase 3 trial required by the FDA, LEQEMBI received full traditional approval by demonstrating its efficacy in treating early-stage AD. (128)

In 2024, Eisai Co., Ltd., and Biogen Inc, continued advancing LEQEMBI's development and regulatory process. The FDA accepted Eisai's Supplemental Biologics License Application for a monthly IV maintenance dosing regimen, aimed at providing a less burdensome option for patients who had completed the biweekly initiation phase. The FDA set a decision date for a Prescription Drug User Fee Act (PDUFA) for January 25, 2025. Furthermore, Eisai initiated a rolling submission for a subcutaneous auto-injector version of LEQEMBI, which received Fast Track designation in May 2024. This version would offer a convenient weekly dosing option, supporting long-term treatment adherence for early-stage AD's patients. (129)

The journey began over 25 years ago with Professor Lars Lannfelt's research, which led to the establishment of BioArctic Neuroscience AB and the of crucial academic partnerships. Eisai's involvement accelerated the drug's progress, while Biogen facilitated its entry into the European market. Figure 4 [10] highlights the key milestones in LEQEMBI's journey, segmented into key phases: "Discovery (1992–2000)", "Early Development (2001–2010)", "Clinical Trials (2011–2020)", and "Approvals & Market Launch (2021–2025)."

LEQEMBI's development exemplifies how biotechnology startups through entrepreneurism can pioneer groundbreaking therapies despite facing regulatory hurdles, funding constraints, and market access issues. The next chapter will explore the critical success factors that enable startups to thrive in life science's dynamic and unpredictable landscape. (76)

[10] **Figure 4 Sources:** (151) (152) (153) (154) (155) (156)

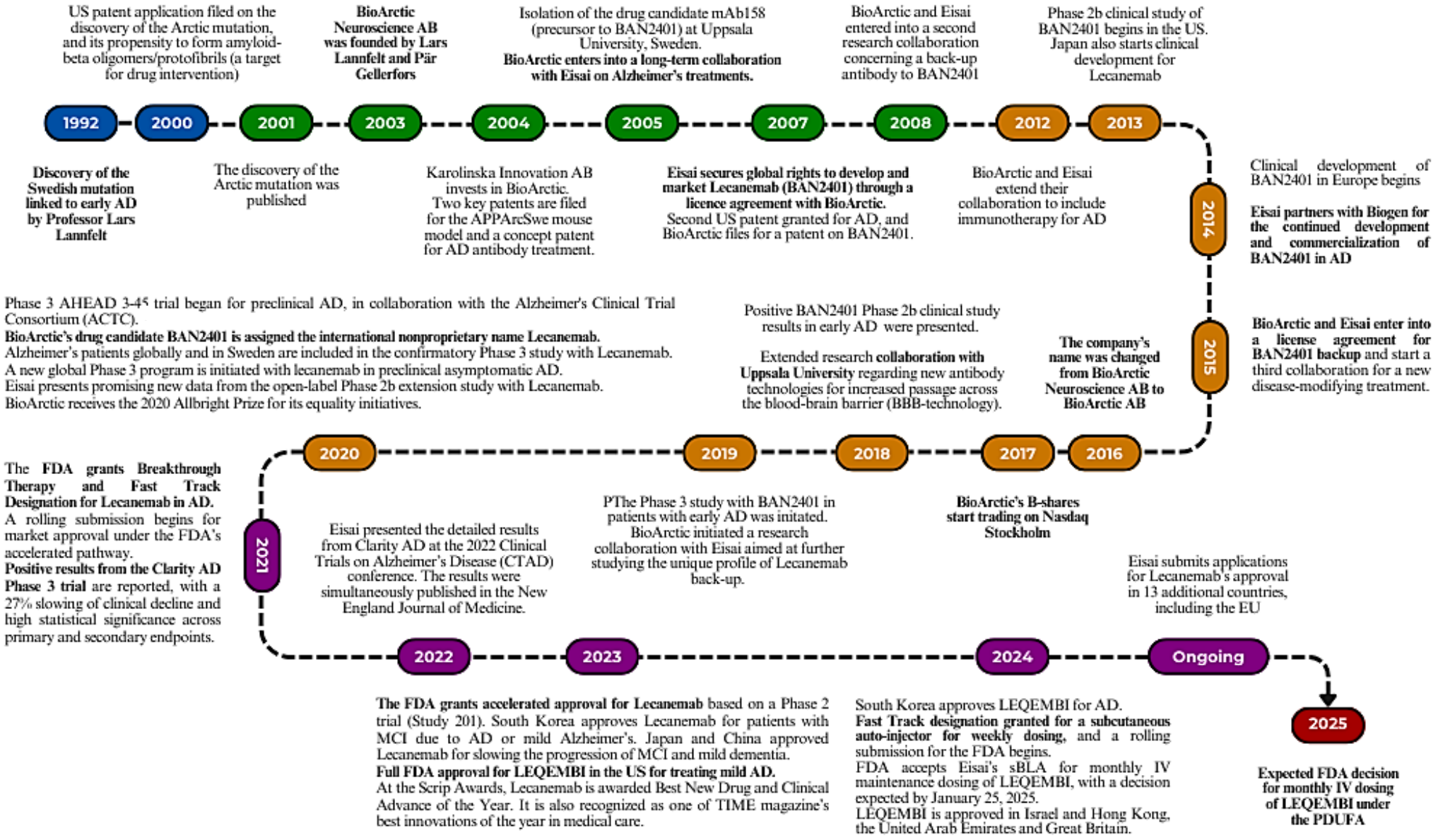

Figure 4. Timeline of LEQEMBI's development and approval.

4.3 *Startups* in Focus

Biotech startups are now key contributors to pharmaceutical innovation, developing many innovative therapies at lower costs compared to traditional pharma companies. The growth of the biopharmaceutical market is fuelled by factors such as the increasing incidence of chronic diseases, an aging population, rising investment in drug R&D, supportive government policies, and the growing global adoption of biopharmaceuticals.

The global biopharmaceuticals market was valued at $571.84 billion in 2023 and is expected to reach $1,183.72 billion by 2032, growing at a CAGR of 8.5%. North America led the market, holding nearly half of the global share at 49.84%, while Europe, the second-largest market, is projected to grow from $57.13 billion in 2024 to $87.47 billion by 2029, with a CAGR of 8.89%. (130,131)

The success of startups is heavily influenced by the intricate innovation ecosystem in which they operate, encompassing enabling policies, access to finance, skilled human capital, supportive research, and strong infrastructure. (82) The U.S. leads the world in the biopharmaceutical sector and exemplifies this complex environment, which includes a variety of key players such as universities, venture-backed startups, and established biopharma companies. Key policies, such as strong IP protection, government funding for basic biomedical research, and a favourable drug pricing system, facilitate significant investment in R&D, creating a vibrant, research-intensive startup landscape. (132)

Recognizing the economic growth and competitive advantage biotechnology fosters, EU too has developed favourable conditions for biotech companies to establish themselves. Two initiative that show this are the Unitary Patent System (UPS) and the Horizon programmes.

The UPS is designed to boost innovation and competitiveness in the EU by streamlining the patent registration process. This system, recently updated, provides a centralized solution for patent registration and enforcement, reducing costs and administrative burdens, especially for small and medium enterprises (SMEs). Through this, innovators can obtain a single “unitary” patent valid across all participating Member States, simplifying the complex national patent laws and validation processes. (133)

Horizon 2020 was the EU's 8th Research and Innovation program, which allocated approximately €76 billion, from 2014 to 2020, to enhance knowledge, skills, and infrastructure while driving economic growth, creating jobs, and addressing societal challenges. In 2021, the

European Commission reported Horizon 2020's substantial impact, having funded nearly 35,000 projects involving 40,000 organizations. Among its notable achievements, the program supported close to 50,000 researchers, significantly boosting mobility, career development, and cross-sector collaborations. Horizon 2020 also enhanced access to large-scale research infrastructure, benefiting over 24,000 researchers and organizations. Its commitment to open access was evident in 82% of its publications being freely available online, fostering knowledge circulation and scientific advancements both within Europe and globally. (134)

Horizon Europe, which runs from 2021 to 2027, is set to invest approximately €93.5 billion, with €10 billion allocated to the European Innovation Council. This council will focus on supporting SMEs, especially start-ups and spin out companies working on transformative innovations, with 70% of its budget designated for this purpose. It offers two main funding instruments: the Pathfinder, which finances early-stage research from initial technology to proof of concept, and the Accelerator, which aids in scaling up innovations from early commercial phases to market launch. This strategy enables SMEs to develop breakthrough innovations through a mix of grants and equity financing. (135)

Figure 5 outlines an example of the cycle of innovation and economic growth U.S. and EU aim to achieve, starting with government/public funding for R&D. In a straightforward way, this funding intends to promote discoveries, the creation of spin-off companies, and private investment, which together drive the development of new drugs. Finally, profits from these drugs create jobs and boost tax revenues, funding further research and perpetuating the cycle.

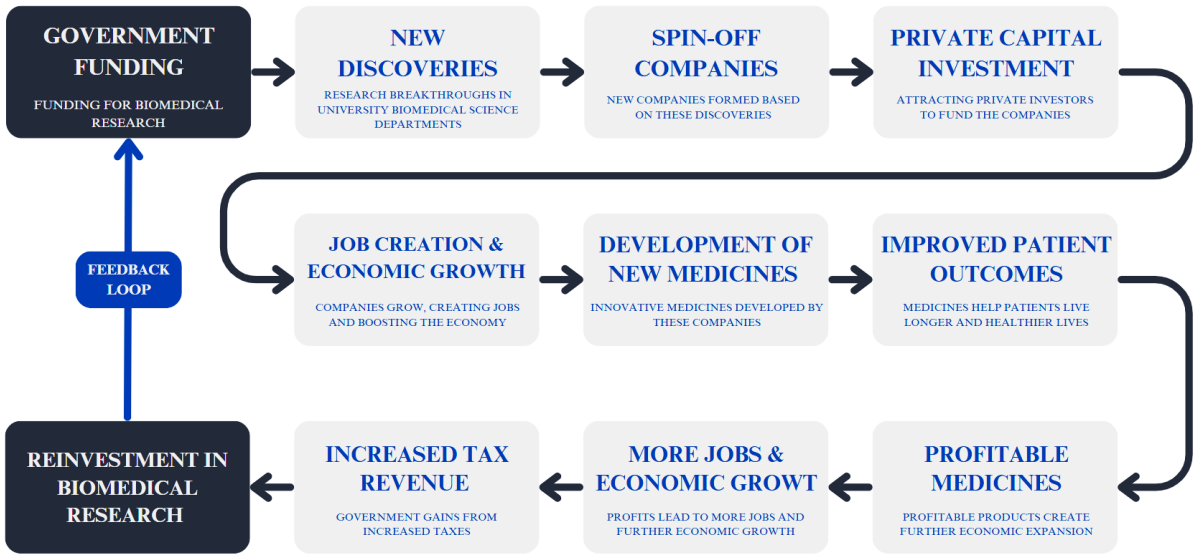

Figure 5. Biopharma Research and Growth Feedback Loop. Adapted from the book "From Breakthrough to Blockbuster - The Business of Biotechnology" p.194-5

Biotech clusters embody these innovation ecosystems by concentrating biotechnology companies, research institutions, academic centres, and support organizations in specific geographic regions. (136) Notable biotech hubs in the US, such as Massachusetts and Northern California, play pivotal roles in this landscape, with Massachusetts home to 152 public biotech companies and Northern California housing 107. These regions not only reflect advanced biotech ecosystems but also showcase impressive market capitalizations[11] - approximately $344.98 billion for Massachusetts companies and around $278.60 billion for those in Northern California. Southern California and New York further contribute to this dynamic, with market valuations of $268.83 billion and $86.50 billion, respectively. Europe also displays significant biotech clusters, with Sweden leading with 79 public companies, followed by the UK (57), France (41), and Germany (23). The latter stands out with the highest market capitalization in Europe at nearly $83.73 billion, largely fuelled by BioNTech's success with its COVID-19 vaccine, Comirnaty. Denmark and Ireland also show strong performances with market capitalizations of $61.53 billion and $41.46 billion, respectively, while the Netherlands, UK, and Sweden report figures of $34.74 billion, $25.78 billion, and $22.10 billion. (137)

Despite the excitement surrounding biotech startups, about 90% fail, with 10% not surviving their first year and 65% folding within a decade. These high failure rates are largely due to the substantial costs of drug development, which make it challenging for biotech companies to secure the equity capital needed to fund their projects without significantly diluting their ownership until they reach commercialization. (138) Among publicly traded biotech companies, the situation is equally challenging; many operate at a loss, with around 25% having less than a year’s worth of capital. All this financial strain creates a precarious environment for startups, emphasizing the need for a deeper understanding of the factors that contribute to entrepreneurial success. (62)

The following chapter explored critical success factors that biotech startups must consider to effectively navigate their unique challenges and enhance their chances of thriving in a competitive landscape.

[11] Market capitalization is the product of a company's share price and the total number of outstanding shares (shares currently owned by shareholders), providing a real-time assessment of its value in the market once it goes public. This valuation is influenced by the dynamics of supply and demand, as changes in share price directly affect the market capitalization. A higher market capitalization indicates a more substantial market presence and greater investor confidence. (157)

4.3.1 Success Factors

Over the past 40 years, the rise of entrepreneurship in healthcare has paralleled the emergence of biotechnology. (139) Entrepreneurs in SMEs and startups have been pivotal in driving health innovation, improving productivity, and making healthcare more affordable. They play a key role in integrating value chain stakeholders—such as suppliers, platform service providers, and customers—through shared business models and data-driven networks. (140) Bioentrepreneurs, often scientists or researchers, utilize their expertise to commercialize innovations, with success driven by opportunity recognition, innovation, and calculated risk-taking. These entrepreneurs rely heavily on technical knowledge and IP management, advancing their own innovations and enabling biotech startups, like BioArctic, to grow alongside the pharmaceutical industry. (56)

Unlike traditional businesses, startups focus on risky and innovative ideas, leveraging the accelerated pace of market change to adapt and improve through the 'Lean Startup'[12] methodology. They have the capacity to disrupt existing markets or industries with their innovative solutions, while also emphasizing the protection and utilization of IP, such as patents, which are particularly relevant in the life sciences sector. They aim to attract investment for growth and often possess the potential for rapid scalability, with a clear business strategy that includes exit options like M&A or Initial Public Offerings[13]. (141)

As illustrated by Figure 6, the startup business plan is complex, requiring careful consideration of a wide array of elements. The challenges faced when developing a startup in the biopharmaceutical or other sectors are essentially the same, contrasting only in their proportions. (56) High failure rate, expensive and time-consuming product development, and strict regulations, intensified by a highly competitive, resource-deprived environment, contribute to this sector's particular intricacies.

[12] The term "lean startup" was introduced by Eric Ries in 2008, who described a startup as "an organization focused on developing something innovative in situations of significant uncertainty." In his book The Lean Startup: How Today's Entrepreneurs Use Continuous Innovation to Create Radically Successful Businesses, Ries elaborates on this concept.

[13] An initial public offering (IPO) is the process through which a private company first offers its shares to the public on a stock exchange, thereby transitioning to public ownership. This mechanism facilitates significant capital accumulation for purposes such as funding expansion or reducing debt, while also allowing private investors—such as founders, angel investors, and family members—to liquidate their holdings and realize returns on their investments. (158)

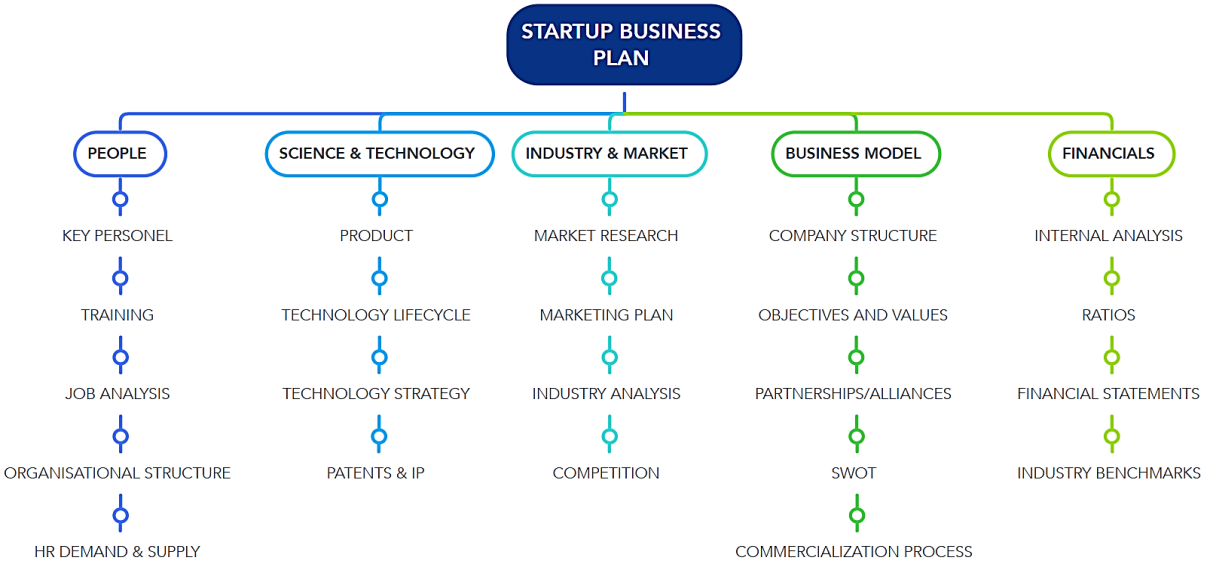

Figure 6. Startup Business Plan. Adapted from the Book "Innovation and Entrepreneurship in Biotechnology – An International Perspective"

Success for biotech startups hinges on several critical factors that are essential for navigating unique challenges and enhancing their chances of thriving in a competitive landscape. Access to capital stands out as vital, as adequate funding allows companies to effectively manage the high-risk nature of drug development, enabling them to support research, development, and operational costs. Additionally, a robust scientific foundation is necessary for transforming innovative technologies into marketable products, establishing credibility and advancing research efforts. Equally important is the ability to attract and retain skilled, motivated employees; fostering an organizational culture that promotes entrepreneurship, adaptability, collaboration, and rapid decision-making. Furthermore, the operationalization of strategy ensures that strategies are consistently evaluated and resources allocated according to commercial goals, maintaining alignment with the company's objectives. Strong managerial skills are crucial for navigating the often challenging transition from research to commercialization—a phase where many organizations encounter difficulties and ultimately fail. By prioritizing these factors, biotech startups can significantly enhance their potential for success, positioning themselves to effectively respond to market demands and regulatory hurdles. (76)

Carolina Reis, in 2017, conducted a systematic literature review and performed interviews with 18 Portuguese startups in the health sector operating within the same ecosystem, with the aim of identifying the success factors for health startups and their main performance indicators. She observed that the most important success factors for entrepreneurs were

primarily six: good control and planning, effective teamwork, differentiation of the product/service, knowledge and capabilities of the staff, adaptability skills, and establishment of partnerships.

Additionally, based on an analysis of 34 significant success factors found in the literature, entrepreneurs emphasized several critical elements as mostly important, including effective record-keeping and financial oversight, substantial working capital, planning, industry knowledge, managerial experience, and the use of professional guidance. Despite this, Reis referred observing a considerable divergence between the literature review and the conclusions drawn from the case studies. She attributed this discrepancy to the limited number of health startups analysed compared to the extensive body of literature reviewed, as well as the unique characteristics of each startup's business model. (142)

Yoshimi Harada, in 2019, also conducted a systematic review to identify biotech startup's success factors. He started by defining success using four performance indicators: achievement of an IPO, M&A, number of products in clinical trials/markets and number of patents. He stated that these are important in determining a startup's capacity to access essential resources, improve product development, and build market presence, all of which are vital to long-term sustainability and success in the biotechnology business.

When analysing the success factors of biotech startups, Harada categorized them into internal and external factors. Internally, a strong management team, along with the founders' expertise in marketing, R&D, and industry knowledge, plays a crucial role. Other important internal factors include strategic direction, market scope, networking capabilities, access to funding, and the companies' age. Additionally, effective supply chain integration and a solid patent portfolio are instrumental in achieving long-term success. Externally, the success of biotech startups is influenced by the overall industry structure, the availability of resources, market dynamism, and the intensity of competition. These external factors shape how a startup can adapt and thrive within a competitive landscape. (143)

Figure 7 provides a comprehensive overview of the previously mentioned success factors for biotech startups. While the literature outlines a range of factors, the composition and capability of the management team, and access to sufficient capital, emerge as particularly critical. A strong management team with relevant expertise is crucial for navigating industry complexities, while adequate funding enables startups to effectively manage the risks associated with drug development. Together, these factors form the essential foundation for thriving in a competitive landscape

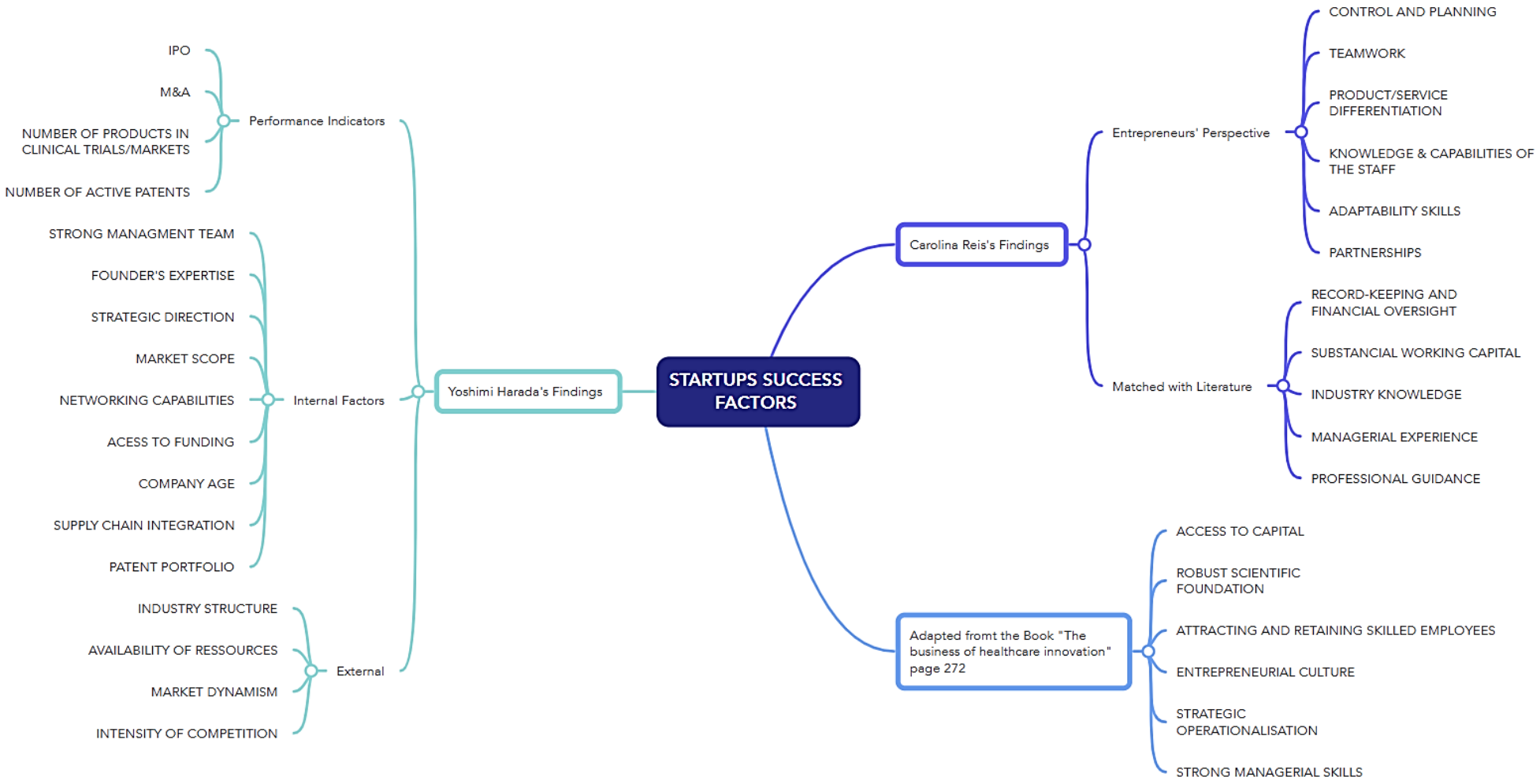

Figure 7. Overview of key success factors for biotech startups, organized by source and theme.

5 Conclusion

This master thesis critically examines the complex dynamics of R&D within the pharmaceutical and biotechnology sectors, highlighting substantial investments and multifaceted strategies that shape healthcare innovation. The staggering €261.4 billion allocated to R&D in 2022—€167.3 billion from pharmaceutical companies—underscores the urgent need for effective strategies in light of the lengthy timelines and high failure rates associated with drug development.

The persistent decline in R&D productivity over the past decade necessitates a revaluation of traditional business models, particularly the Blockbuster model, which struggles against patent expirations and generic competition. The example of Eli Lilly's Prozac, which saw a 70% market share loss post-patent expiration, exemplifies the critical need for innovation beyond established paradigms. This master thesis demonstrates that adopting Open Innovation Models has become a vital strategy for pharmaceutical companies to sustain profitability and drive innovation.

Outsourcing has emerged as a critical strategy for pharmaceutical companies, enabling them to collaborate with CROs like Syngene International, which partnered with GSK in 2018 to expedite drug candidate discovery. Furthermore, strategic R&D collaborations with academic institutions, such as Pfizer's research centre near MIT and Harvard, significantly enhance access to cutting-edge research, driving breakthrough innovations. M&A strategies are another widely used model, allowing firms to expand their portfolio by acquiring assets at a late clinical stage. In-licensing agreements are also vital, enabling pharmaceutical companies to bolster their pipelines with innovative drugs and technologies from biotech innovators in exchange for royalties. Additionally, CVC has gained traction, with firms like NVF managing over $750 million to support early-stage biotech startups in North America and Europe. These open innovation models are essential for the industry to meet evolving healthcare needs and navigate financial and operational challenges, fostering a collaborative approach that sustains innovation amid competitive pressures.

The last five decades have marked a transformative era in biotechnology, characterized by significant capital investment and groundbreaking innovations. Startups like Moderna and BioNTech, which utilized mRNA technology for COVID-19 vaccines, as well as all the innovative therapeutic approaches in development, exemplify how biotech can deliver lifesaving therapies swiftly. As we look to the future, oncology and neurology remain priority

areas for investment and innovation. The FDA's recent approval of LEQEMBI for early Alzheimer’s treatment, stemming from a biotech startup's efforts, demonstrates the power of entrepreneurial innovation in addressing critical healthcare challenges.

As this thesis illustrates, biotech startups play a crucial role in driving pharmaceutical innovation and developing therapies at lower costs than traditional firms. The growth potential is immense with the biopharmaceutical market projected to reach $1,183.72 billion by 2032, t. Bioentrepreneurs will continue to leverage their scientific expertise to commercialize innovative ideas, focusing on high-risk concepts and employing methodologies like the 'Lean Startup' to thrive. Additionally, their success will rely on access to capital, strong scientific foundations, and effective team management. By fostering these ecosystems, we can unlock the full potential of biotechnology, ultimately transforming patient care and improving global health outcomes.

This exploratory work emphasizes the vital role of open innovation and entrepreneurship in shaping the future of global health and ensuring the resilience of the pharmaceutical industry. It clarifies the complex relationship between the pharmaceutical and biotechnology sectors and their collective influence on healthcare advancement. However, due to the broad range of topics covered, this study adopts a generalized perspective, prioritizing an overarching view over a detailed analysis of specific elements. For instance, other open innovation models such as incubators, PPP, crowdsourcing, open-source initiatives, and virtual R&D were not examined. Additionally, many innovations, technologies, startups, and critical funding topics like IPOs—essential to startup development—were not deeply referenced.

Rapid advancements in artificial intelligence, digital health, the Internet of Things, and blockchain are increasingly important for the biotechnology and pharmaceutical industries. By promoting open innovation and supporting startup growth within strong innovation ecosystems, the industry can address complex healthcare challenges and develop transformative therapies. Thus, the collaboration between these sectors offers significant potential for future healthcare improvements.

Future research should delve deeper into these emerging trends, providing a foundation for scholars and stakeholders to enhance their understanding and effectively tackle evolving healthcare issues to improve patient outcomes.

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