Challenges and Opportunities in Biotherapies and Bioproduction - an EIB Investment Perspective

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The field of biotechnology is characterized by rapid advancements and breakthrough innovations. This dynamism poses unique challenges. The need to keep up with technological advancements, regulatory requirements, and shifting market dynamics demands substantial financial commitments and a forward-thinking approach. Although investment in advanced therapies has reached a record high of over $20 billion/year in 2020 and 2021, venture capital investment in biotech declined by 30-40% in 2022. Given the sector's strategic importance, the European Investment Bank (EIB) is committed to playing a major role in developing a resilient and zero-emission biotechnology and bioproduction industry. The Bank is supporting the field with a holistic approach across the entire value chain, from raw material supply to research, development and bioproduction. The EU bank is the biggest venture debt provider to the life sciences sector in Europe with a portfolio of over €2.7 billion, supporting more than 100 innovative companies, almost half of which are in the biotechnology space.

Biotechnology is a rapidly expanding field with strategic implications not only for medicine and health but for Europe's competitiveness, security and economic resilience. This year marks the 70th anniversary of the ground-breaking discovery of the double helix structure of DNA by James Watson and Francis Crick in 1953[1]. This breakthrough revolutionized our understanding of the genetic code, leading to the development of powerful scientific techniques such as recombinant DNA research, genetic engineering, and gene sequencing, ultimately paving the way for precision medicine which can tailor disease prevention and treatment for individuals according to their genes, environments, and lifestyles.

Although humankind has been using biotechnology processes since ancient times to make bread, cheese and wine, the history of modern biotechnology in medicine involving genetic engineering and cell manipulation kickstarted in 1973, when scientists first genetically engineered Escherichia coli bacteria to express a foreign gene that made them resistant to an antibiotic[2]. This revolutionized the way biological molecules obtained through genetically engineered bacteria, yeast, fungi, cells or even whole animals and plants[3] are produced and triggered a paradigm shift in how we tackle diseases.

Broadening prevention, diagnostic and therapeutic options over conventional chemistry-based small molecules to more sophisticated and targeted biotherapies based on biotechnology products, the field has been expanding constantly and biologics – drugs made from or containing components of living organisms – in 2022 accounted for a higher share of the new medicines approved by the US Food and Drug Administration (FDA) than small molecules, the first time in history. Since the approval of the first advanced therapy medicinal product (cell, tissue and gene therapies) by the EMA in 2009[4], these treatments have become increasingly significant to patients, the industry, and healthcare systems, as acknowledged in the "Pharmaceutical Strategy for Europe"[5].

(1) Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid | Nature J. Watson and F. Crick, 1953, https://www.nature.com/articles/171737a0

(2) Construction of Biologically Functional Bacterial Plasmids In Vitro - Herbert Boyer & Stanley Cohen, 1973, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC427208/

(3) Biotherapeutic products (who.int), https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/biotherapeutic-products

(4) ChondroCelect, autologous cartilage cells for the treatment of cartilage disease.

(5) European Commission. Pharmaceutical Strategy for Europe, 2020, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0761

Barriers to investment

Despite their potential and the recent high-profile successes of biotech companies like BioNTech, whose novel mRNA vaccine helped to turn the tide against the Covid-19 pandemic, many factors still limit private investment in the sector.

The field of biotechnology is characterized by rapid advancements and breakthrough innovations. This dynamic nature poses unique challenges for investments in biotherapies and bioproduction. The need to keep up with technological advancements, regulatory requirements, and shifting market dynamics demands substantial financial commitments and a forward-thinking approach.

Biotherapies and bioproduction are also subject to stringent quality standards and regulatory frameworks to ensure their safety and efficacy. Navigating these regulatory hurdles poses a significant challenge for investors. Compliance with regulations, such as good manufacturing practices (GMP) and regulatory submissions, adds complexity to the investment process, requiring extensive expertise and resources. The fact that global regulatory frameworks are not fully harmonised, adds yet more complications and uncertainty for potential investors.

Another factor is Intellectual property (IP) protection, which plays a crucial role in biotechnology investment. Developing and maintaining robust IP portfolios is vital to safeguarding innovations and ensuring competitive advantages. However, the complexities of patent laws and the potential for patent disputes pose challenges for investors, as the security and exclusivity of their investments rely heavily on intellectual property rights.

Capital-intensive and long development timelines

Other factors that impede investment in the sector stem from the length, capital intensity, and uncertain nature of the development process.

The beginnings of the modern biotech industry are commonly traced back to the US, when Robert Swanson persuaded the scientist behind the recombinant protein invention, Herbert Boyer, to co-found a new company called Genentech with a $1.000 joint investment in 1976. Genentech was later bought by Swiss pharma company Roche for $46.8 billion in 2009.

Today, however, biotechnology is a field where developments are lengthy and costly and where associated risks are high. According to Deloitte, the average cost of developing a new drug among the top 20 global biopharmas rose by 15% ($298 million) in 2022 to $2.3 billion[6]. Moreover, it takes an average of 10-12 years for a new biological drug candidate to be developed from bench to market approval, far beyond the typical five-six year investment horizons of private venture capital firms. These long development times erode the potential revenue streams offered by initial patents, which decreases the potential return from the investment in their research and development.

This makes it challenging for early-stage biotech companies to raise capital even from investors used to supporting start-ups. Although investment in advanced therapies has risen sharply over the last few years, reaching a record high of over $20 billion/year in 2020 and 2021, venture capital investment in biotech declined 30-40% in 2022. This was mostly due to a reluctance among venture capitalists to invest in new start-ups, rather than on building up the ones already in their portfolios. External factors, such as inflation and a decreased availability of financing, have also contributed to a decline in biotech investment, including those in regenerative medicine. In 2022, investment in regenerative medicine, a growing filed in the biotech industry, dropped to $12.6 billion, returning to pre-pandemic levels.

Uncertainty is the other major obstacle. Investments in biotechnology carry inherent risks and uncertainties, particularly regarding expected levels of return. The risk of clinical trial failures remains high in this market and in addition regulatory approval of a new therapy, a sine qua non condition towards patients' use, is not a guarantee of good market penetration and sales for a biotech. Evidence requested to biotech companies to demonstrate the added value of newly approved biotherapeutics to cost-constrained healthcare systems is also increasing developments costs. Due to their cost, the vast majority of patients may not receive cell and gene therapies, as stakeholders struggle with successful business models that would allow approved medicines to bring good returns for shareholders and companies. Given their relatively high costs and complex manufacturing requirements, cell and gene therapies pose a daunting commercial challenge to drug companies and healthcare providers.

As a result, many advanced biotech therapies have struggled commercially despite their therapeutic potential. Safety concerns and the limitations of the gene editing capabilities of first-generation cell and gene therapies have hindered their broader use. Moreover, the ever-increasing costs of advanced therapies and the difficulties in securing reimbursement from national health or insurance schemes are already having a negative impact on the successful adoption of biotech innovations in standard care. Five treatments have been withdrawn from the EU market since 2010, largely due to commercial reasons.

Potential investors in biotech also need to contend with many uncertainties that could have an impact on their expected return on investment. One is the amount that national health schemes and insurers are willing to reimburse patients for these treatments. The market for precision medicine treatments is by definition much smaller, which tends to mean higher prices and implies a different business model. To ensure a worthwhile return on investment, drug producers need to ensure that their products are adequately reimbursed so that patients can afford them.

[6] Pharma R&D return on investment falls in post-pandemic market, Deloitte report, Jan. 2023.

The advanced manufacturing (bioproduction) processes involved in the latest generation of biotherapies, such as cell and gene therapies, tend to be challenging to scale up, making it more difficult to reach full-scale production and reap the benefits of cost savings which would lower prices and lead to greater use. The nature of biotherapy supply chains from manufacturer to patient, are also complex and multidisciplinary, especially for cell and gene therapies.

Europe's fragmented equity markets – European biotechs are listed on 15 different European stock exchanges, with 90 percent listed in their home countries – are also a disadvantage because it makes it harder to develop a knowledgeable investor base for the sector.

Investing in European biotech

Given the sector's strategic importance to the European Union, the European Investment Bank is committed to playing a major role in developing a resilient and zero-emission biotechnology and bioproduction industry.

The EIB has provided total financing of more than €42 billion for healthcare-related projects around the world since it started investing in the sector in 1997. Financing has risen considerably since the pandemic. In 2022, for instance, the Bank provided €5.1 billion for health and life sciences projects – money that will benefit around 980 million people worldwide. In addition, the European Investment Fund (EIF), a subsidiary of the EIB Group that specialises in providing risk finance to small and medium-sized businesses, committed some €400 million to funds that are expected to support the health sector[7].

One of the tools that the Bank uses for biotech firms is venture debt[8], a special kind of loan to an early-stage company that provides liquidity to a business between equity funding rounds. Venture debt is particularly well suited for biotech because it can help to fill the market gap for scale-up financing for high-growth, innovation-focused companies, without diluting existing shareholders. It's an important tool to assist firms heavily involved in research to continue to invest in research and development and market expansion. The EIB has utilised venture debt to support select investments in biotech, new technologies and strategic technology development in areas like drug development and green energy. These research-focused companies have limited access to standard debt financing due to a low asset base and not yet having reached profitability. Lack of sufficient collateral and asymmetric information are among the two largest market failures preventing young and innovative SMEs from accessing traditional bank-lending.

[7] Health Overview 2023 (eib.org), https://www.eib.org/attachments/lucalli/20220314_health_overview_2023_en.pdf

[8] Venture debt (eib.org), https://www.eib.org/en/products/equity/venture-debt/index.htm

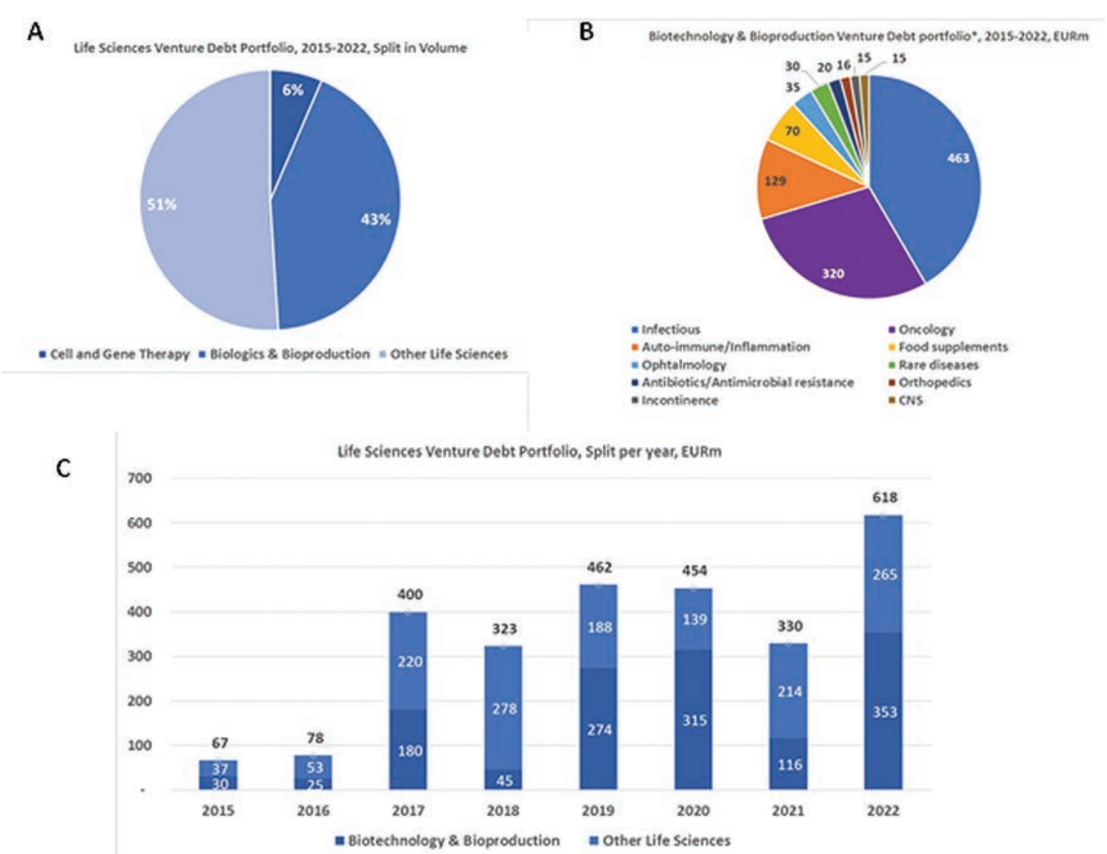

Figure 1. EIB's Life Sciences Venture Debt portfolio 2015-2022, (A) split by volume (%), (B) by indications, and (C) by year. In (B) the financing of Evotec was not included due to the company's activities covering several indications.

Another advantage of the EIB's venture debt is that it helps companies to attract other investors. By providing venture debt loans to highly innovative companies operating in the health sector, the EIB mobilizes at least 1.4 times as much financing from other investors. On average, for every euro loaned by the EIB, another €1.37 flows into the financed venture debt projects from other sources.

Since the introduction of the venture debt product in 2015, the EIB has become the biggest venture debt provider in Europe in the life sciences sector with a portfolio of over €2.7 billion, supporting more than 100 innovative biopharmaceutical and medtech companies. Almost half of these investments were dedicated to companies in the biotechnology space, specifically 43% in biologics and bioproduction and 6% in cell and gene therapy projects (Figure 1A).

The EIB has pursued a 360-degree investment strategy across all indicators, with infectious diseases and oncology benefitting from the largest support (Figure 1B). The overall trend of EIB investments in the life sciences and biotech space has been steadily increasing over time, with the highest volumes in 2022 (Figure 1C), further supporting the sector beyond the pandemic in an effort to revive declining investments in the field. With many companies needing extra cash to cope with the level of inflation, the EIB, like other investors in the field, is also considering providing additional financing to companies already in its portfolio.

As the climate bank of the European Union, the EIB ensures that all its financing activities, including the venture debt that it offers to the biotech sector, are aligned with the principles and goals of the Paris Agreement, a commitment that builds a pathway towards low greenhouse gas emissions and climate-resilient development.

Conclusion

When it comes to healthcare, the market struggles to allocate resources efficiently. Market distortions can arise from the failure of investors to recover costs despite generating an overall economic benefit for society. As a result, healthcare may lack resources, with serious consequences for individuals and communities.

The EIB has been involved in mitigating this situation using a range of financing instruments including project investment loans, project financing, investment programmes and framework loans as well as venture debt. In some cases, the Bank also contributes with equity.

The EIB has a strong portfolio in the life sciences and biotechnology investment spaces and is committed to funding innovative European projects at the forefront of technology, including the new wave of precision medicine, regenerative medicine, cell and gene therapy. The Bank is supporting the field with a holistic approach across the entire value chain, from supply to bioproduction. The EIB has played a strong and catalytic role during the pandemic and its success stories in the field, such as BioNTech, demonstrate its commitment to the sector. The Bank serves as a vital public institution for the life sciences and biotechnology sectors and continues to evolve in order to address the ever-changing challenges posed by this field.

Case study: BioNTech

Many European biotechs that the EIB has supported have gone on to achieve great things and some have even gained unicorn status. BioNTech headquartered in Mainz, Germany, is today the most valuable biotech company in Europe. While the company works on a wide range of technologies, including antibodies and CAR-T cell therapy, it rose to public fame in 2020 as the first company to commercialize a messenger RNA (mRNA) Covid-19 vaccine together with its big pharma partner Pfizer. Today, over two billion doses of the company's vaccine have been administered around the world.

The BioNTech financing is one example among dozens that show how venture debt from a public bank is important in helping companies in the infectious disease sector get to the later stages of development. The private sector is reluctant to invest in this part of the economy, because companies are often startups or have little track record and the eventual success of any innovation is hard to predict.

The EIB had signed a €50 million loan with BioNTech in December 2019 to help the company work on cancer treatments and was impressed by the company's team. The Bank signed another loan, worth €100 million, in June 2020, after an accelerated approval that concentrated into two months a process that normally takes longer than a year. This loan, backed by guarantees from the EU budget through the InnovFin Corporate Research Equity programme and the European Fund for Strategic Investments, was designed to help BioNTech's vaccine trials and manufacturing.