



**Opportunity
on your doorstep:
A guide to investing in
the UK biotech sector**



September 2020

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Forewords

Steve Bates OBE

CEO, UK BioIndustry Association

The importance of the biotech industry has never been clearer. As the sector mobilises to find solutions to the COVID-19 crisis, there is acute interest from governments and much of the public across the world. We all now depend on effective medicines, diagnostic tests, and ultimately a vaccine, to get economies and our normal lives going again.

The UK sector has been at the forefront of the global collaborative effort. Its science, people and companies are world class. The University of Oxford's Jenner Institute and UK-based pharmaceutical giant AstraZeneca are among the frontrunners in the vaccine race, using technology owned and developed by UK-based Vaccitech. At the end of July they published clinical trial results showing their candidate elicits an immune response and shows no safety concerns. Elsewhere, Oxford Nanopore has developed hand-held technology that can perform 15,000 fast, accurate and low-cost COVID-19 tests a day, and Southampton-based Synairgen has shown its therapy can drastically reduce instances of severe symptoms in COVID-19 patients.

These are just a few of the many hundreds of other studies underway within biopharma companies to develop COVID-19 solutions. Throughout the crisis, the UK Government and our sector have worked collaboratively to address this challenge for society. A leading life sciences venture capitalist and former BIA board member, Kate Bingham, was put in charge of securing the UK's vaccine supply, such is the belief in our sector's abilities.

The sector's heightened strategic role – not just during this outbreak, but almost certainly after it, too – has not escaped investors' attention either. Biopharma and healthcare is one of the few economic sectors to have largely escaped the market meltdown brought about by COVID-19. UK biotech was outperforming the broader market before COVID-19 hit; since then its relative performance has been stronger still. The Nasdaq Biotech Index in the US is riding a five-year

high. Several companies' share prices also hit all-time highs; AstraZeneca became the most valuable company on the London Stock Exchange.

Most pundits agree that the world will never be the same again, even after lock-downs are lifted. Health policy will change, as more money is invested in health systems to allow for better pandemic preparedness. Diagnostic testing is likely to play a much greater role in public health. Medicines that can be taken at home and/or self-administered may become more valuable. Many aspects of healthcare provision, such as GP consultations, may remain online. Surveys show that doctors and patients prefer tele-consultations in many circumstances, and are unlikely to revert to prior levels of in-patient visits.

No one knows precisely what society will look like post-COVID-19. But the biotech sector will certainly feature even more prominently as the source of medical innovation to maintain and improve health, and to protect us from future pandemics.

We've written this guide to help those who see the value and potential of biotech, and the UK sector in particular. It has two aims: the first is to help demystify biotechnology for non-specialist investors; the second is to provide practical guidance on how to invest in the sector, and thereby participate in the next exciting and revolutionary advances in human, animal and environmental health. Now is a great time to take a deeper look at the opportunity. We hope you find this guide helpful.

Denzil Jenkins

Interim CEO, London Stock Exchange plc

In his forward, Steve Bates has highlighted the vital role being played by the United Kingdom's biotech industry these unprecedented times. The extraordinarily agile response by the industry to the pandemic, both in terms of vaccine development and production of testing and diagnostic equipment, has been nothing short of astonishing.

Our biotech industry is truly world class and will remain at the forefront of global industry efforts to develop and make widely available vaccines to keep Covid-19 at bay and medicines to treat those affected by it. Behind this, there are the many UK businesses that feed into the system, such as reagent suppliers, outsourced drug trial and development specialists, medical device manufacturers and so on.

London Stock Exchange is honoured to support this vital industry and those wishing to invest in it.

The Biotech and associated Healthcare sector is a significant component of the London equity market with, currently, 109 companies listed on our Main Market and AIM that, between them, have a cumulative market value of £248 billion.*

AIM is Europe's leading growth company market, accounting for 68% of growth equity capital raised in the first quarter of 2020 alone.* Now in its 26th year, AIM is designed to support growth companies and has a range of associated tax benefits available for investors, be they private individuals (directly, or via retail trading facilities), family offices, wealth management groups or Venture Capital Trusts, through to the more mainstream institutional funds. AIM is currently home to 85 sector companies.

The Main Market has currently 24 sector companies listed, ranging from the relatively small, through to the largest, including those in the benchmark FTSE100 and FTSE250 indices. As Steve Bates recognises AstraZeneca has become the most valuable company on the London Stock Exchange.

The strength of the London market and the companies listed on it is reflected in having the most international split of institutional investors amongst the major global exchanges: around half are drawn from the United Kingdom and a third from North America, showing that London listed companies attract interest globally.*

The growing interest in the sector by all investor types is reflected in it being the best overall

performer since the beginning of the year and at end of June was up by an overall 46%**.

A key role for us is supporting companies to raise new capital. Since the start of the year, companies already listed on our stock markets have between them so far raised £26.5 billion of new equity across 427 transactions.* Of this, £2.4 billion has been raised by sector companies across 50 transactions.*

We have also worked with various of the United Kingdom's financial regulatory authorities and market participants to provide companies with more flexibility around fund raising and financial reporting to reflect the challenges of working during the Covid-19 crisis.

London Stock Exchange is at the forefront of promoting retail investor participation in publicly-listed shares, through, variously: helping companies communicate more widely with existing and potential shareholders using our dedicated on-line Spark portal, together with a growing range of informative webinars and podcasts available on our website. We have also been working with PrimaryBid (www.primarybid.com) to help facilitate wider retail investor participation, via their digital platform, in Initial Public Offerings and follow-on issues by companies already listed on our markets.

Finally, our efforts do not just involve publicly-listed companies and those that may seek to list. Our Elite (www.elite-network.com) scale-up programme is working with a growing number of private companies, helping them to plan and achieve their chosen paths to commercial success, as well as fund raising.

Looking forward, we will continue to provide every assistance to those companies listed on our stock markets and to welcoming those that will choose to list in London and raise the funding so vital to the continuing progress being made by the industry to protect and help us all.

Data as at * 21 Aug 2020 and ** 30 June 2020

**Written by Melanie Senior, Healthcare Writer
and Analyst and Martin Turner, Head of Policy
and Public Affairs at the BIA.**

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Pinsent Masons



For more information about the BIA and our finance work,
please contact info@bioindustry.org.

Introduction

Biotechnology was enjoying a golden age even before COVID-19 hit. The pandemic has further highlighted the crucial role this sector plays in global health – and confirms its strategic importance over the long-term. Rapid progress in our understanding of the molecular and genetic bases of life is unleashing extraordinary new opportunities across medicine, energy, manufacturing, materials and more. Many of biotechnology's products have already transformed our world and they will continue to do so beyond 2020. This sector holds many of the solutions to today's most urgent global challenges, from fighting pandemics and climate change to building sustainable energy and industrial production systems. Investment is required to deliver these solutions; in return, investors can reap financial, social and ethical rewards.

Biotechnology is no longer the new kid on the block. This 30-year old sector now includes mature, revenue-generating companies, as well as innovative start-ups building new technologies, and new business models. Record levels of private and public investment poured into biotech over the last decade and the sector also enjoys strong government support in many countries. This is only set to continue after the pandemic.

All investors should consider biotechnology as part of their growth portfolios. Ignoring it would mean missing out on one of the most important financial and impact investments of the new decade.

This guide has two aims: the first is to help demystify biotechnology for non-specialist investors. The second is to provide practical guidance on how to invest in the sector, and thereby participate in some of the most significant improvements in human, animal and environmental health.

It does not provide investment advice or seek to promote any individual financial product.

Executive summary

This guide to investing in biotech is primarily focused on the sector's role in improving healthcare. Yet biotechnology's products are helping to solve an expanding range of societal and industrial challenges that reach well beyond healthcare. Scientists' growing understanding of biology is converging with advances across technology, data science and engineering to open up opportunities across almost all industrial sectors. Engineering biology is developing cleaner fuels, more environmentally friendly foods and fabrics, more efficient manufacturing and more 'intelligent' materials, to name but a few examples. Many of the principles described in this guide in relation to drug-development companies apply equally to all biology-enabled tech businesses.

The past twenty years have seen some of the most exciting and significant advances in biotechnology and medicine. Chief among them was the sequencing of the human genome at the turn of the century, which unleashed over the following decades a much deeper understanding of the complex genetic, molecular, behavioural and environmental components of health and disease. These advances have generated tools and technologies that are now enabling more personalised medicines, including cell and gene therapies that are tailored to the needs of individual patients or patient groups. Science is providing hope to patients with conditions that until now have had no treatments at all. It is also leading to more accurate and accessible diagnostics that can help catch some diseases early, when they can be more effectively addressed.

Demand for healthcare is growing as populations age. Expanding middle classes are demanding the latest innovations. Global spend on medicines is set to reach \$1.1 trillion by 2024, according to IQVIA. Yet the large, multinational pharmaceutical companies that distribute most medicines across the globe are developing fewer new drugs in-house. That is making them eager buyers of biotech assets, which account for a growing majority of the overall drug development pipeline. These therapies are at the cutting-edge of science and focussed on treating patients for whom there are currently no other available treatments.

Meanwhile, the digital revolution that has already transformed so many aspects of society is also changing health and healthcare delivery. The COVID-19 pandemic accelerated several existing trends, including toward online or phone-based physician consultations, and 'virtual' clinical trials where patients are monitored at home. Health data collection and analysis is booming, helping drive a better understanding of the causes and course of disease, and what constitutes good health. Wearable sensors, health-related apps and services are empowering consumers to take more control of their wellbeing, and vastly expanding healthcare's global reach. The fast-evolving consumer health market explains the well-established presence within healthcare of technology giants Apple, Google and Amazon. This changing healthcare landscape will provide many further opportunities for biotech companies.

The extraordinary growth in medical knowledge, in the global demand for healthcare and the expanded uptake of digital health tools provide compelling reasons to consider investing in biotech. The positive ethical and social impacts of the sector provide further benefits beyond the financial returns.

Granted, discovering and developing new treatments for unmet healthcare needs is risky and expensive. Most experimental therapies do not make it all the way to market; those that do may face pricing and reimbursement hurdles. But several of the same forces driving the revolution are also helping reduce those risks and costs. One is personalised medicine. Pre-selecting the patients most likely to respond to a given treatment – using a companion diagnostic to identify a particular genetic mutation, for instance – increases the odds of that therapy proving effective. It is also likely to do so more quickly, and potentially with less capital expenditure than would have been required for a less selective treatment.

Biotech investors can reap their rewards well before drug approval, though. The pharmaceutical sector's growing appetite for biotech products means they are not just paying more for such assets, but they are also doing so earlier in the development cycle, with activity driven by stiff competition. That means biotech investors can generate outsized returns, but with reduced capital demands and within shorter timeframes. The constant demand for healthcare, which is often paid for by governments and insurance companies rather than consumers, means that the sector is also insulated from the vagaries of economic cycles.

This guide seeks to demystify this exciting sector for the curious and uninitiated investor. The first chapter explores the transformative power of biotech and the broadening range of applications and business models, which allows investors to find opportunities to suit their risk appetite and diversify their exposure.

The second chapter explains the R&D process, regulatory landscape, healthcare market dynamics and the different routes to financial returns for biotech investors.

The third chapter reveals the great opportunity on our doorstep. UK-based scientists and biotechs are world-leading, supported by a broadening, more international investor base, and led by experienced management teams. These strengths have been underscored by the UK contribution to the COVID-19 response.

The fourth and final chapter outlines different ways to invest in the biotech sector – from buying individual company shares, to spreading risk through the growing range of collective investment vehicles. Each route comes with advantages and disadvantages that investors must weigh up.

The time is ripe to explore the UK biotech investment opportunity. We hope you find this guide a useful first step in your journey.

Biotech delivers benefits across industrial sectors

Biotechnology is impacting almost all industrial sectors. New, more targeted medicines are saving lives; cleaner fuels are helping sustain our planet, and more efficient, cleaner manufacturing processes are transforming economies across the globe. The biotechnology sector includes many types of companies, and a wide range of business models.

This chapter provides an overview and introduction to biotechnology, its subsectors and diverse business models.

What is biotech?

Biotechnology is biology-driven technology. It uses biological processes to develop products, systems and tools that can help improve our health and reduce our environmental footprint. The products of biotechnology include new medicines to fight disease, cleaner manufacturing processes, more efficient food production and much, much more.

Humans have for thousands of years used natural biological processes like fermentation to make bread and alcohol and to preserve food. Greater understanding of our own biology, and that of micro-organisms like yeast and bacteria, has in turn widened biotechnology's products and their applications.

The biotech industry emerged in earnest during the late 20th century, as the knowledge and tools required to modify living organisms matured. An important landmark came in 2001 when scientists, many of whom were based at the UK's Wellcome Sanger Institute, sequenced the entire human genome – the chemical instruction booklet for a human being. This Human Genome Project marked the start of an extraordinary period of biological discovery, from which the rewards are now emerging.

Over the last two decades, scientists have learned much more about our genes, and about how they deliver their instructions for building and maintaining us.



The glossary on page 55 provides definitions for technical terms in this guide

They have also started to unpick how and when things go wrong and cause illness. This knowledge has enabled the design of more effective medicines, including many for previously un-treatable conditions. Genomics – the study of our genes – has opened up novel, more personalised treatments, such as cell- and gene-therapies. It has also led to more powerful diagnostic tests that can pick up the signs of disease much earlier.

This deeper understanding of biology and biological systems is also creating new industries and helping satisfy consumers' and investors' demands for greater sustainability. Taking inspiration from processes and organisms found in nature, biotechnologists – alongside engineers and computer scientists – are programming bacteria to generate cleaner fuels, helping reduce our reliance on petroleum-based products. They are transforming food production, quality and distribution. They are enabling more environmentally-friendly industrial manufacturing, processes and products.

How can biotechnology improve health?



Earlier identification of disease risk and diagnosis, through genetic screening



Disease prevention through more effective and better targeted vaccines



Faster drug development and more accurate drug delivery



New treatments for previously untreatable conditions, e.g. engineered tissue, stem cell therapies

How can biotechnology improve the world we live in?



Lower environmental pollution with bio-degradable plastics and plastic-digesting bacteria



Reduced reliance on fossil fuels through biologically-produced chemicals and fuels



More efficient food production with engineered crops and improved fertilisers



Novel high-performance materials for fashion, sports and construction industries

The BIA has published a range of guides to different sub-sectors of the biotechnology industry. They can be found on the BIA website at: www.bioindustry.org/policy/strategic-technologies.html

Box 1: Innovation that has driven the biotech boom is also driving the rapid global response to the COVID-19 pandemic

Biotech's role in the global response to COVID-19 has highlighted the sector's critical importance in the modern world.

Biopharma companies, academic institutes and scientists across the world mobilised at breakneck speed to develop solutions to the pandemic. These solutions – diagnostics, medicines and vaccines – are central to governments' abilities to safely re-open their economies.

The sector's extraordinary response led to over 100 treatments and more than half-a-dozen vaccine candidates in clinical trials by mid-May 2020, just months after full lock-down began. Promising Phase I data emerged on 18 May from the vaccine candidate of US biotech Moderna just eight weeks after the trial began, and four months from the entire programme inception. Oxford's Jenner Institute and AstraZeneca are among the front-runners in the vaccine race, using technology owned and developed by UK-based biotech Vaccitech, having published results at the end of July showing their candidate elicits an immune response with no safety concerns. The global pipeline includes hundreds of pre-clinical programme, including a candidate at Imperial College London that is based on different technology to the Oxford/AstraZeneca candidate, showing the value of having a diverse science base allowing multiple shots on goal.

Treatments are also in development, with some ready for patients. On May 1, US biotech Gilead Sciences' anti-viral remdesivir received emergency use authorization¹ from the US Food and Drug Administration for patients with severe COVID-19 symptoms, and approval from the UK's regulator on 26 May.² As with vaccines, there's an array of candidates in pre-clinical and clinical development being progressed by multiple UK and global companies.

There has also been a flurry of activity to develop diagnostic tests for the virus. These efforts include tests that can detect current infection levels ever more rapidly and accurately, as well as antibody tests that assess whether individuals have developed immunity.

The range of individual programme, and the speed at which they are advancing, also showcase the extraordinary scientific and technological advances of the last decade or more, alongside the sector's creativity, resourcefulness and determination. Genetic sequencing tools enabled the virus' genetic code to be analysed in days, rather than months. Extensive online data-sharing meant multiple teams across the world could get to work.

Several vaccine candidates, including those of Moderna and Imperial College London, are based on RNA, a type of genetic material that offers a promising new approach to treatment and vaccination. The treatment pipeline also includes cell therapies, alongside small molecules and antibodies. New gene editing tools such as CRISPR feature in diagnostic tests for COVID-19. Multiple other existing therapies are being investigated to see if they work against the virus; remdesivir was originally developed to treat the Ebola virus, for example, but showed more promise in the coronavirus-based SARS and MERS outbreaks in 2002/3 and 2012, respectively.

This wave of COVID-19 related innovation has come about thanks to a rapid acceleration in the processes of discovery, development and regulatory approval. Drug development timelines – typically measured in years or even decades – have been condensed into months or even weeks. Adaptive trial designs, for instance, allow studies to be modified after they have begun, offering greater flexibility and speed. Regulators have supported such approaches, including, in some non-COVID-19-related trials, the use of remote monitoring and other digital technologies. Digital health tools were already gaining traction across the industry before COVID-19 arrived; now they are front-and-centre.

This collaborative effort from stakeholders within industry, academia, and the wider community, supported by governments and deploying cutting-edge science and technologies, may do more than win the battle against this virus. It could lay the groundwork for greater effectiveness, inclusiveness and efficiency across drug R&D, and across healthcare delivery.

Biotechnology is transforming medicine

Medicine is where the biology-driven revolution is farthest along and so the focus of this guide. Biotechnology is making medicine more personalised, and thus more effective. It has created entirely new types of medicines that work in ways unlike anything that has come before (see Box 2).

Most drugs on the market are effective only in a subset of the patients that take them. Personalised or precision medicine is changing that. Researchers and physicians use diagnostic tests to identify particular genetic or biological markers that tell them which therapies are most likely to succeed. Personalised medicine is ramping up development success rates and improving patients' outcomes.

Cancer dominates personalised medicine, for now. The runaway cell growth characterising this often-deadly disease is caused by a range of genetic mutations, some of which can be targeted by personalised medicines such as Lynparza (olaparib). Lynparza – discovered by UK-based biotech firm KuDOS, later acquired by AstraZeneca – is particularly effective in patients with BRCA gene mutations. It is used in patients with advanced ovarian, breast and pancreatic cancer.

Personalised medicine is expanding to other therapy areas too. Chronic illnesses like heart disease, diabetes and dementia are also being sliced into ever-narrower sub-types as scientists begin to uncover some of the multiple genetic mutations and downstream molecular processes that influence these conditions.

Genomics-related advances across biotechnology have also deepened scientists' understanding of the genomes of other organisms, including both disease-causing and friendly bacteria. New avenues have opened up in the anti-microbial drug R&D – a field traditionally lacking investment, yet which is likely to see a lot more post-coronavirus.

Meanwhile, the trillions of micro-organisms residing in our gut – the gut microbiome – is now believed to influence many of the most widespread, chronic conditions afflicting society today. Even more recent discoveries of the links between the gut, the immune system (much of which resides in the gut) and the brain are opening up further fertile territories for innovative drug discovery, including in some of the most difficult-to-treat conditions such as dementia.

Biotechnology is making medicine more personalised, and thus more effective.

Box 2: Not all drugs are alike

Medicines come in many forms (also known as modalities). These have evolved over time, with there generally being considered three waves.

First wave	Second wave	Third wave
1950s	1990s	Today
Small molecule drugs, market dominated by large pharmaceutical companies	Large molecules (antibodies and enzyme replacement treatments) market dominated by pharmacy and US biotech	Advanced biologics and diagnostics in areas such as gene therapy, cell therapy and DNA sequencing. Typically targeted to specific well-defined patient populations. Opportunity for market innovation and disruption
		

Small-molecule drugs refer to chemical compounds synthesized in the laboratory or extracted from plants or other organisms. They are usually taken as pills, and include established products like aspirin, penicillin or beta-blockers, as well as many newer medicines, including some targeted cancer treatments. Small molecules were at the heart of the pharmaceutical industry as it emerged during the 19th century from apothecaries and chemicals companies.

Large molecules or ‘**biologics**’ are proteins produced from microbes or cell cultures. These molecules are usually too large to be delivered in pill form, so they are often injected. The biologics category began to mature during the 1990s, and since then have accounted for a growing proportion of the biopharma pipeline.

Antibodies (an important category of biologics) are proteins that fight off invading pathogens by seeking out and targeting tell-tale molecules, called antigens. Our bodies produce their own antibodies, but biotech allows us to “design” new ones as medicines.

Gene therapies replace a faulty or missing gene with a working copy. The healthy gene is delivered using a carrier system, often a harmless virus. This enables the cells to work properly again, alleviating disease symptoms.

Cell therapies are made from patients’ own cells. These cells are engineered outside the body to combat a particular disease, and then re-injected into the patient.

Vaccines protect against particular diseases. They contain agents, or the genetic code for agents, that are similar to a disease-causing micro-organism (a bacterium or virus). These teach the immune system to effectively fight the illness. Some vaccines are therapeutic – designed to treat, rather than prevent, disease.

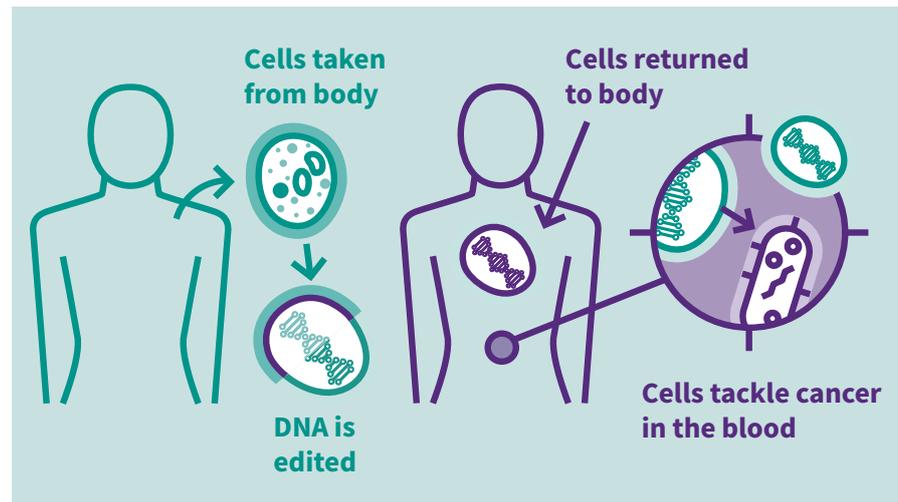
Immuno-therapy involves harnessing the body’s immune system to fight disease. Its greatest impact has been in cancer, since the disease’s ability to hide from the immune system is what enables it to spread so rapidly and dangerously. Cancer immuno-therapies include a range of drug types, and work in a variety of ways. Some are antibodies that attach to cancer cells to flag them up to the immune system. One example is breast cancer treatment Herceptin (trastuzumab). Other immuno-therapies interfere with immune-system proteins that hamper the system’s cancer-fighting ability. These ‘checkpoint inhibitors’ include Merck’s Keytruda (pembrolizumab) and Bristol Myers Squibb’s Opdivo (nivolumab). Cell therapies, vaccines or genetically-modified viruses may also be immuno-therapies.

The next generation of therapies

Cell and gene therapies are prominent examples of the new kinds of medicines that biotechnology has delivered.

Advances in our understanding of the role of genes in disease are helping uncover hitherto unknown or under-recognized disorders, including many rare genetic diseases. Gene therapies work by correcting or replacing faulty or missing genes found to be responsible for certain illnesses. They are different to conventional pills or injectable drugs, since they address the underlying cause of a disease (see Box 2). Gene therapies are already changing the lives of many patients with debilitating, often fatal diseases. Some may offer a potential cure.

Cell therapies, like some gene-therapies, are tailored to particular patients rather than mass-produced like most mainstream drugs. Cell therapies are made from patients' own cells. These cells are engineered outside the body to combat a particular disease, and then re-injected into the patient.



Many experts believe that cell and gene therapies represent the next significant therapeutic category since the advent of humanized and fully-human monoclonal antibodies thirty years ago (see Box 2 and Glossary). Regulators have approved the first handful of cell and gene therapies for various rare conditions including some aggressive cancers, having created special pathways for them.

Most cell and gene therapies, as well as many other medicines addressing rare and serious conditions with no currently-available treatment, are classified by regulators as 'orphan' medicines. They enjoy fast-track development and approval pathways, additional years of market exclusivity, plus various financial and tax breaks in some countries. On average, the estimated R&D cost of an orphan drug is around 27% of the cost of a non-orphan.³ Incentives are intended to make investment in their development more favourable and help explain the growth in the number of orphan drugs on the market, and in company pipelines.

Box 3: UK leadership in the next generation of therapies

In 2019 there were more than 70 companies developing cell and gene therapies in the UK, 25 manufacturing facilities, and three unicorn companies that have each reached over \$1 billion in value.⁴ The number of UK clinical trials grew by 37% compared to 2018, with an increasing

number of trials sponsored by commercial organisations. Ten new cell and gene therapy spinouts emerged in the UK in 2019 alone – a credit to the supportive UK ecosystem, which includes development, manufacturing and clinical adoption.

Cancer immuno-therapy is another rapidly-growing and increasingly valuable treatment category. Immuno-therapies work by harnessing the body's own immune system to fight off cancer; they include a range of drug types, including antibodies, cell therapies and small molecules (see Box 2 and Glossary). 'Immune checkpoint inhibitors' are antibodies that unlock certain mechanisms that cancer cells use to evade the immune system. There are several marketed checkpoint inhibitors and many in development. Some are targeted at tumours with particular genetic mutations, regardless of their location in the body.

Biotech offers various company models and risk-profiles

Many biotech companies focus on discovering and developing new medicines. These groups offer investors a high risk, high reward profile: they typically have significant R&D costs and are initially loss-making. Yet those with promising programmes can generate high returns for investors, for instance via licensing fees, an IPO or an acquisition. Those rewards may materialise well before a product reaches the market (and may be realised even if the therapy ultimately fails).

Healthcare-focused biotechnology companies are not only discovering and developing new therapies, however. Many are developing diagnostic tests, or providing the tools, services or data systems necessary to support drug R&D. A growing sub-category is building digital health products and services that combine the best of medicine and consumer technology (see Box 4).

Box 4: Medical biotech company types

Drug discovery biotechs are those discovering (and sometimes going on to develop) potential therapies. The capital investment may be significant; the rewards if a product candidate succeeds can be much, much higher. Healthy returns may be achieved well before product approval if R&D progresses well and the company is able to go public, or is acquired by another company (usually a large pharmaceutical company). The multiples achieved will depend on the market climate (for IPOs), the asset(s) in question and the therapy area.

Pros: *Huge gains if an asset is approved and/or if earlier R&D success triggers a sale, IPO or other exit opportunity.*

Cons: *High capital demands and the downside of a binary outcome: asset failure.*

Diagnostics companies develop tests and tools for diagnosing disease. Sometimes, diagnostics are used to identify patients that can benefit from a particular drug; these are “companion diagnostics”.

Pros: *Lower clinical risk than for drug R&D-based companies: determining whether a test is sufficiently sensitive and specific for a given condition/biomarker. Diagnostics may be used in R&D and/or on commercial market. Diagnostics use is growing as personalised medicines gain traction and as the value of testing has been highlighted by COVID-19.*

Cons: *Reimbursement can be challenging as some payers are reluctant to pay for products that are not therapies. IP protection is often less robust than around therapeutics, meaning lower barriers for competitors entering the market.*

Platform-based companies develop technologies that may, directly or indirectly, generate a range of product candidates, often across multiple therapy areas. The technology can be licensed to discovery – or development-focused partners, generating revenues that can fund an in-house pipeline.

Pros: *Option to generate licensing revenues, helping meet the cost of product R&D. Platform approach provides multiple shots on goal.*

Cons: *In-house pipeline may progress slower due to licensing activities, delaying product-based upside. Technology may fail or become obsolete.*

Service-based companies provide services to drug discovery and development partners. These may involve designing or running pre-clinical studies or clinical trials, the use of a particular technology, approach, software and/or data analytics tool, manufacturing, and more. Genomics has un-leashed a range of new service opportunities, from designing ‘promoter’ sequences to directing how and when DNA is translated into proteins, to analysing vast amounts of genomic data.

Pros: *Low-risk, regular revenues; opportunity to become supplier of choice in particular domain. Sale and IPO opportunities remain.*

Cons: *Less likely to generate the large returns associated with product success.*

Leaner, less capital-intensive company structures also help mitigate financial risk and can shorten timelines for investors unwilling or unable to invest over longer timeframes. Asset-centric models focus on advancing a particular programme, with no (or limited) company infrastructure. ‘Virtual’ companies, similarly, may be run from investors’ premises, with leased laboratory space. Both can rely heavily on outsourcing R&D to other companies and universities, reducing capital costs and accessing the best talent and resources wherever they are located globally.

There are similar models and breadth within industrial and agricultural biotech, offering investors plenty of opportunity to diversify holdings and to spread risk while capitalizing on the opportunities offered from an ever-increasing understanding of biology.

Diagnostics

Diagnostics enable the early screening, disease prevention and therapy-targeting that are key to health system sustainability. As seen with COVID-19, diagnostic testing is critical in monitoring and curtailing the spread of infectious disease. Personalised medicine is enabled by accurate diagnostics, to determine which drug is best for which patient.

The COVID-19 pandemic and the growth of personalised medicine are both driving renewed interest in diagnostics. The pandemic has highlighted the value of testing for active infection and of testing for immunity to the infection. Such ‘serologic’ testing detects antibodies produced by the immune system to fight off the virus. Both kinds of tests are needed to contain and manage the pandemic. Many companies, large and small, are working on providing such tests and on making them as accurate and as accessible as possible.

In drug R&D, diagnostic tests are increasingly developed alongside particular medicines, helping identify the patients most likely to respond to particular therapies. Such ‘companion diagnostics’ help reduce ineffective, wasteful or even harmful use of medicines, and are already improving drug development success rates.

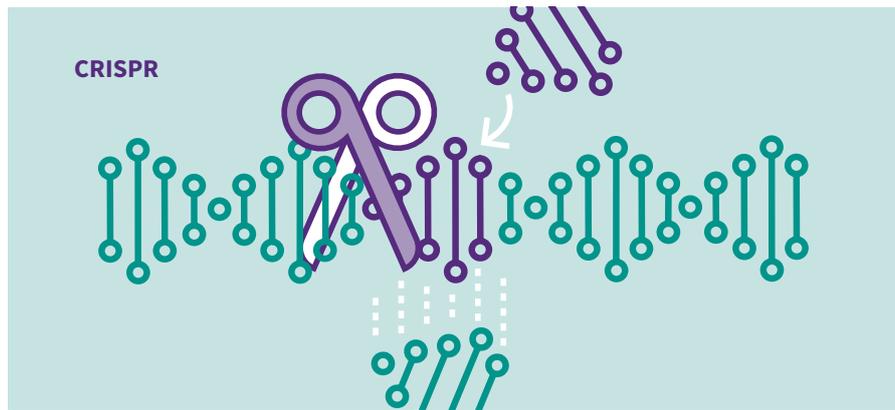
Companies are working on novel diagnostic tests that may be able to detect very early signs of cancer, before symptoms appear. These could help prevent the disease, or at least reduce its severity, significantly impacting many patients’ lives, as well as health system budgets. Other diagnostic approaches use health data analytics to determine patients’ risk of contracting a particular condition, such as chronic kidney disease, allowing closer monitoring and prevention.

Diagnostics is a growth area with distinct regulatory and reimbursement pathways, and with commercial dynamics that differ from those of therapeutics. This provides investors with a means to spread risk.

**Companion
diagnostics are
improving drug
development
success rates.**

Tools, services and data

Biotechnology's extraordinary productivity and potential come in large part thanks to better, more accessible tools to explore, edit and exploit genetic material and biological processes. The gene editing technology known as CRISPR-Cas 9 is one recent and potentially-revolutionary example. It allows scientists to target, remove and insert certain sections of DNA as if using molecular scissors. Other tools may enable faster, more accurate or more cost-effective gene sequencing, or better ways to control which genes are expressed. Many of these tools are relevant across industrial and agricultural biotechnology too, and companies that develop them might supply a broad market.



Genomics may be rooted in biology, but it is fundamentally about data. The study of genes and the molecular mechanisms through which they influence physical characteristics, including disease, is generating vast swathes of data. Collecting, analysing and making sense of these huge datasets is a multi-disciplinary challenge that has created a large market of companies developing and selling analytical tools, systems and software to drug developers as well as to other companies across a range of sectors.

That's why data science now pervades biotech R&D. It may accelerate some aspects of discovery and development, but is also generating new kinds of products. Artificial intelligence (AI)-enabled diagnostic imaging is a reality, and so are 'digital therapeutics' – evidence-based software solutions, often delivered via smartphone, to help prevent, manage or treat various diseases. Examples of such therapies (which are subject to regulatory approval) include Pear Therapeutics' reSET app for substance use disorders. The first version was cleared by the US FDA in late 2017; the app aims to reproduce aspects of cognitive behavioural therapy for clinician-supervised patients, who may also be taking medication.

Digital is transforming healthcare and the life sciences

Kerry Baldwin

IQ Capital

Kerry Baldwin is Managing Partner at IQ Capital, which invests in UK-based technology companies, typically at seed or Series A stage.

“IQ Capital sees huge potential for digital transformation across healthcare and the life sciences. This change is being driven by several converging technology themes – big data handling and computation, AI analytics (such as image-processing, machine reading, and graphical modelling), automation of “-omics” technologies, and embedded biometric sensors. The UK is a leader in some of these technology areas, and we are already seeing several disruptive start-ups in medical imaging, drug discovery and clinical trials management.

“The UK government recognises the value that a strong tech ecosystem brings to the wider economy and has enacted multiple policies to encourage STEM entrepreneurs. This support, plus the modernisation of university technology transfer activities and policies has helped create a vibrant ecosystem of local tech clusters across the UK.

“The translation of tech innovation into UK healthcare has been held back for a number of reasons, including the navigation of complex regulatory hurdles, resistance to behavioural change among healthcare professionals, and the generally slow pace of new technology adoption within the NHS. However, these bottlenecks are steadily being addressed. Initiatives such as the i4i programme, Wellcome Trust’s Health Innovation Challenge Fund, and the University of Edinburgh’s Digital Health and Care Institute are driving forward the digital health ecosystem. In parallel, the UK Government is setting up organisations such as NHSX and NHS Digital, with the aim of driving digital transformation within healthcare.”

Healthtech and digital health

The convergence of healthcare and technology has created a new sector, closely related to biotechnology but with distinctive characteristics. “Healthtech” or “digital health” is a loosely-defined category that includes companies generating health-related data, and building data infrastructure, systems and analytics. It also encompasses groups designing wearables or sensor-based technologies that straddle the consumer/retail and healthcare markets. Wrist-worn activity trackers, smart-phone-based heart-rate monitors and electrocardiograms, or blood-glucose sensing patches linked to user-friendly software for patients with diabetes are just a few examples. A growing number of such products are endorsed by the medicines authorities (e.g. smart-watches that can detect atrial fibrillation). Lesser – (or un-) regulated wellness-based products continue to proliferate too, including DNA-sequencing services that purport to generate dietary or broader healthcare advice, ancestry information and, in some cases, genetic-based disease risk.

As tech companies like Google and Apple dive into various corners of healthcare, digital health is similarly drawing in investors traditionally focused on software and information technology. The appeal is a growing healthcare and wellness market, greater consumer awareness, shorter development timelines and lower development risks than conventional drug R&D. Digital is also transforming the delivery of healthcare, from app-based doctors' appointments or medication adherence support tools, to home-based vital-signs monitoring of patients with chronic diseases, or remote, smartphone-based diagnoses, for example of eye- or skin-conditions.

COVID-19 accelerated the adoption of digital health technologies, as patients, physicians and other healthcare stakeholders were forced to rely on online consultations. Many believe some of the tools used during the pandemic will remain popular thereafter, as their cost and convenience advantages become clearer and as familiarity and confidence build.

Industrial and agricultural biotech

Industrial biotechnology harnesses biological processes and resources to transform how materials, chemicals and energy are produced. It is a big part of the solution to many of our most pressing global challenges, from environmental damage to food security and the depletion of natural resources.

Biotechnology is helping deliver cleaner, more sustainable manufacturing processes. For example, bacteria are being engineered to digest the toxic waste products of industrial processes, or plastic drinks bottles. Scientists are producing biodegradable chemicals and plastics, plus novel textiles, such as engineered spider-silk protein, that are both practical and sustainable. They are enabling less toxic fabric-dyeing techniques, and new manufacturing methods such as 3D printing. Industrial biotechnology is deriving new energy sources from biomass – plant-derived materials such as sugarcane or forestry residues – that can, if properly managed, be carbon-neutral.

Innovators are even exploiting the unique structure and behaviour of the tiny DNA molecules that make up our genes to develop new “intelligent” materials and components, like gas-sensing nano-wires, nano-scale batteries or anti-counterfeit “quantum-inks” for secure documents.

COVID-19 accelerated the adoption of digital health technologies.

Biotechnology is also used in agriculture to help improve crop yields and nutritional value, and reduce dependence on environmentally-damaging fertilisers and pesticides. It can also help make crops more resilient to drought, flooding and other external stresses, as climate change threatens many parts of the world. These advances in the efficiency and sustainability of the food supply chain are crucial in the face of population growth and finite resources.

Box 5: Biotech as an ESG investment

Investors are increasingly demanding evidence of companies' environmental, social and governance (ESG) commitments. Biotechnology scores highly in this regard and can contribute positively toward investors' ESG goals.

The sector creates many of the new medicines and technologies that improve individual and population health. Life expectancy has been increasing steadily since the mid-19th century, but one of the fastest increases came during the 15 years following 2000, during which a full 5 years was added to global life expectancy.⁵ Much of that increase came thanks to improvements in public health, medical care and diet. Pharmaceutical and biotech companies are partners in international alliances to increase access to medicines and vaccines in developing countries, such as Gavi, the vaccine alliance, and the Global Fund to Fight AIDS, tuberculosis and malaria. The sector provides medicines and vaccines at lower cost to developing countries, or awards voluntary licenses to allow the countries to manufacture the products themselves.

Biotechnology is at the heart of the quest to develop cleaner, more sustainable energy, food, materials and manufacturing processes. Industrial biotech as a whole could reduce CO₂ emissions by up to 2.5 billion tonnes per year, according to a report from the World Wildlife Fund (WWF).⁶ Already, the global sector helps avoid the creation of 33 million tonnes per year, through various applications, while only emitting 2 million tonnes.

As a relatively young industry, staffed by highly-educated employees, biotechnology also does well on employee work conditions and equality. Biotechnology (along with pharmaceuticals and organic fine chemistry) has among the highest numbers of female inventors – about half of patents filed between 1998 and 2017 named at least one female.⁷ The number of female innovators worldwide has doubled over the last two decades. However, it is widely recognised within the sector that more must be done to improve diversity. The BIA supports this through Women in Biotech events, to build networks and promote mentoring, and it is working with the charity In2science to provide work placement and careers guidance opportunities within the industry for young people from disadvantaged backgrounds so that they can achieve their potential and progress to STEM and research careers.

The use of animals is an emotive but essential aspect of the drug R&D process. Testing the toxicity of prospective medicines in animals is a legal requirement. The UK has some of the world's most robust regulations for the use of animals in R&D, to ensure that they are only used where strictly necessary and that their suffering is minimised. The industry supports this strong regulation and also invests in the replacement, reduction and refinement of the use of animals in research (known as the 3Rs), primarily through the UK's National Centre for the 3Rs. More information can be found at: www.nc3rs.org.uk

What to consider when investing in biotech

Biotechnology offers investors many exciting companies to choose from and the opportunity to build a diverse portfolio. But it is also a complex sector, with several unique aspects that investors need to understand.

Focusing on healthcare, this section sets out the basics of how drugs are discovered, developed and commercialised, typical biotech company trajectories (including exit options), and the most common valuation techniques.

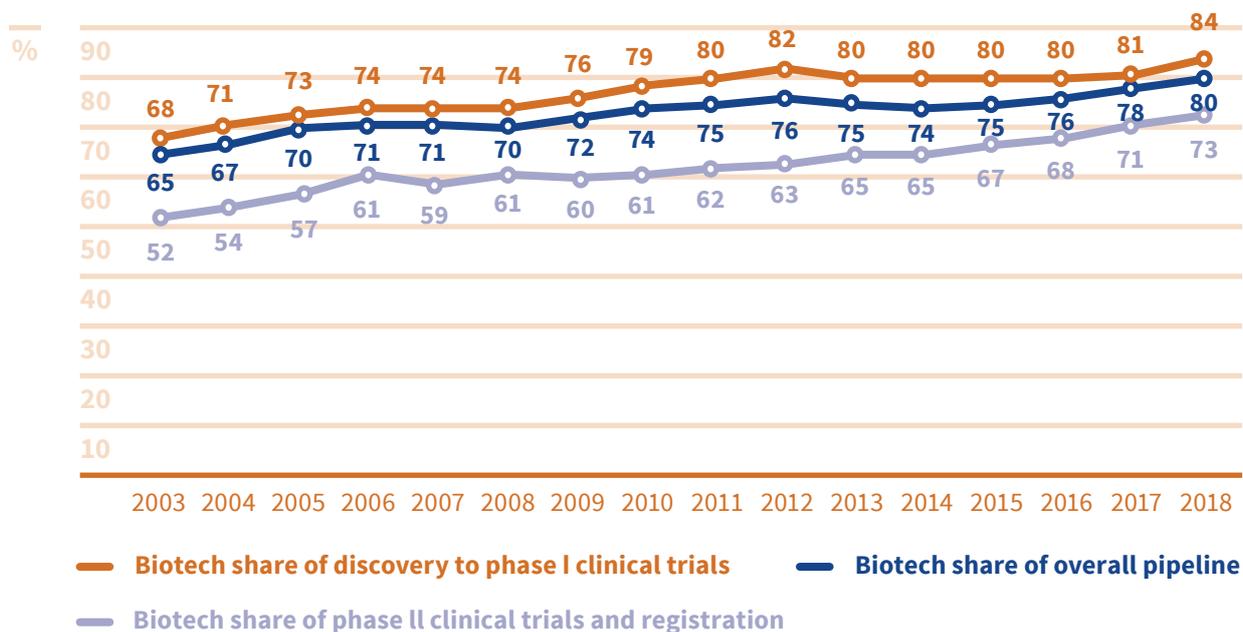
It also outlines key considerations for potential investors. These include companies' stage of development, therapy area or disease focus, as well as broader, industry-wide trends. Although the focus is on healthcare, many of the principles apply to other biotech subsectors.

Biotech dominates the medical innovation pipeline

Biotech companies are increasingly dominant in the global search for the next generation of medicines, replacing their older and larger pharmaceutical forebearers.

In 2018, biotech companies accounted for 80% of the potential medicines in the global clinical pipeline (see Figure 1).⁸ Biotech companies also accounted for the vast majority of highly-specialised medicines, such as biologics, personalised medicines and gene therapies, in late stage development around the world.

Figure 1: Biotech* accounts for a large, and growing, share of the development pipeline



Source: IQVIA Pipeline Intelligence, Jan 2019⁹

*Defined here as companies spending less than \$200m on R&D, or with revenues under \$500m

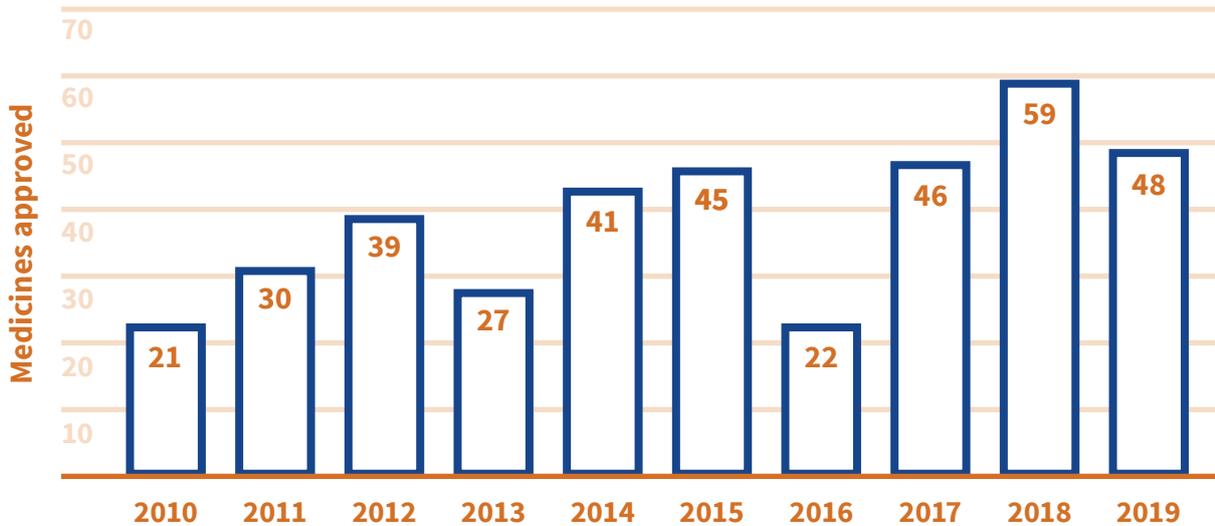
The global drugs market is growing rapidly

Global medicine spending is projected to increase at 2–5% annually and to exceed \$1.1 trillion in 2024.¹⁰ This growth is driven by two key factors.

The first is ageing populations in developed countries, and a growing middleclass in emerging economies. Between 2014 and 2018, the Brazilian, Chinese and Indian pharmaceutical markets grew by 11.4%, 7.3% and 11.2% respectively.¹¹

The second driver is the rapid increase in the number of biologics, targeted medicines and other highly-specialised therapies, which command high prices and are overwhelmingly developed by biotech companies. Annual new drug approvals by US and European regulators have been trending upwards for most of the last decade, even though 2019's totals were slightly below those in 2018 (see Figure 2).

Figure 2: More new medicines are being approved than ten years ago

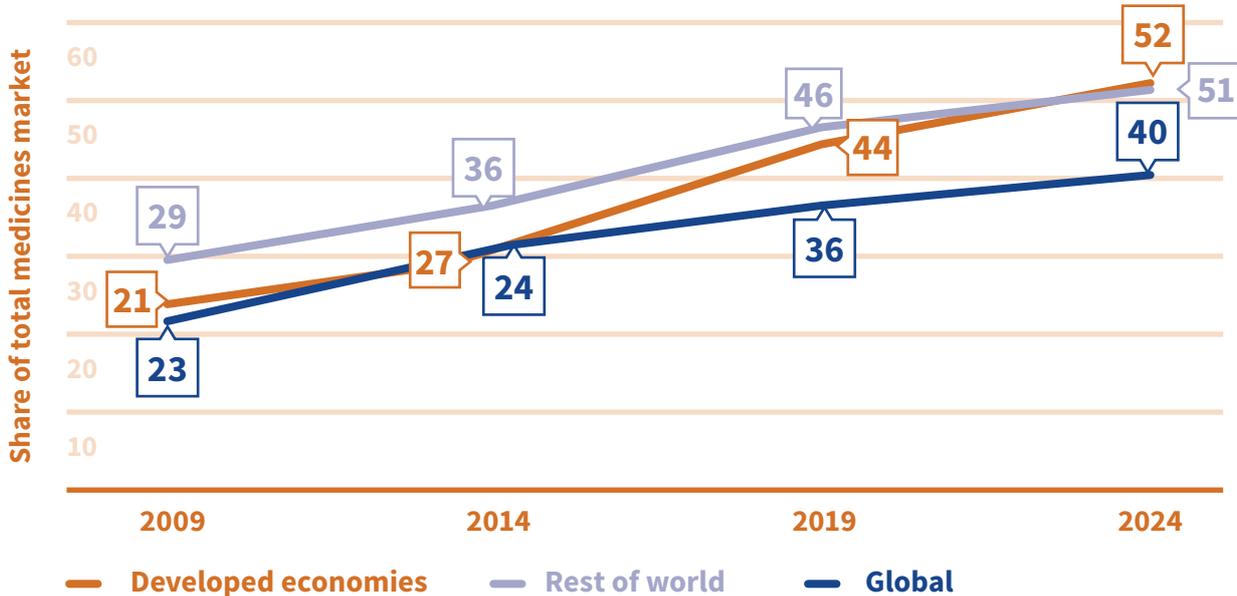


Source: US Food and Drug Administration (Center for Drug Evaluation and Research approvals only)¹²

Over the next five years, an average of 54 novel medicine launches are expected annually. Two-thirds of launches will be specialty products for chronic, complex or rare diseases.¹³ That will rise to almost 50% the share of spending on such therapeutics by 2024 in most developed markets¹⁴ (see Figure 3).

Biotech companies are operating in an expanding market, with high and growing demand for their unique products. Those fundamental drivers have not changed post-COVID-19; arguably they are even stronger. Unmet needs remain, and populations are still ageing, even as the wider economic impact of the pandemic introduces uncertainty into forecasting drug approval rates and market growth.

Figure 3: Speciality medicines are becoming a more significant part of healthcare markets across the globe



Source: IQVIA Market Prognosis, Sept 2019, IQVIA Institute, Dec 2019¹⁵

The R&D and regulatory processes

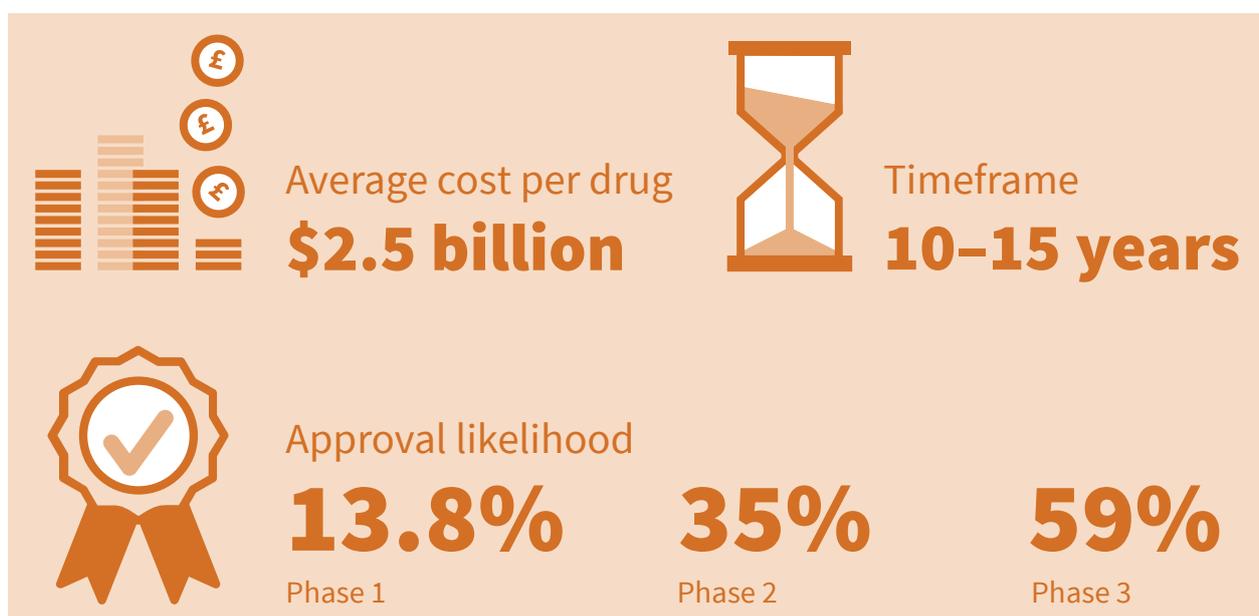
R&D is at the heart of the biotechnology industry. It is expensive, risky, and can take many years. This means R&D-focused companies often face long periods of high capital spend before any meaningful revenues are achieved (unless the asset is licensed or sold along the way – see 35). The outcome of drug R&D is usually binary: success, or failure. Success can translate into considerable returns; failures are costly. However, there are instances where drugs that prove ineffective in one setting achieve huge success in another. Famously, Viagra was initially investigated – unsuccessfully – as a treatment for heart disease.

R&D typically involves research (in the laboratory), followed by pre-clinical testing (usually in animals) and clinical development (in humans). The final “Phase III” stage of clinical development usually supports registration and regulatory approval (see Box 6).

Taking a drug from discovery through to market approval may take 10–15 years and cost over \$2.5 billion, according to the Tufts Center for the Study of Drug Development.¹⁶ However, as explored elsewhere in this guide, these figures vary considerably and advances in knowledge and technology is bringing down both metrics. In exceptional circumstances, those timelines may become radically shorter, as seen during the COVID-19 pandemic, when the urgent need accelerated the development of several medicines and vaccines.

In normal times, fewer than 14% of all drugs in clinical trials make it through regulatory approval, according to a 2018 study by the MIT Sloan School of Management. Prior estimates were even lower, at between 9–11%.¹⁷ As an asset progresses through development, the risk of failure reduces and the asset’s value will usually rise.

These data are averages; they should not be used to forecast the chance of any individual drug’s approval. Specialist data providers and analysts can help investors better assess the chances of R&D and regulatory success for specific drug candidates.



Box 6: The R&D and regulatory process

Research

Research (or discovery) refers to early work carried out in the laboratory to discover or design molecules that may influence the course of a disease.

Pre-clinical development

In pre-clinical development, a drug candidate undergoes further tests, often in animals, to help elucidate its mechanism of action and effects, both positive and negative. Drug candidates that make it through pre-clinical testing without showing unacceptable signs of toxicity, or lack of efficacy, then enter the clinic for clinical trials.

Clinical development (clinical trials)

Phase I: safety. Healthy individuals are given the experimental drug to determine how the body tolerates it and what side-effects it may cause.

Phase II: efficacy and safety (small-scale). The drug is tested in a small number of patients with the condition to determine if it has the desired effect and what side-effects it may cause. This is also the point at which different doses are tested.

Phase III: efficacy & safety (large-scale). Phase III trials include a sufficient number of patients to generate statistically meaningful safety and efficacy data to support eventual regulatory approval. This is the longest and most expensive stage of development.

Clinical trial design

Before each Phase I or II clinical trial is started, researchers will set the endpoints, which are the outcomes that must be achieved for the trial to be considered successful. Trials will often be reported as having met their endpoints (succeeded) or missed their endpoints (failed). However, even when an endpoint is missed, further detailed analysis of the data may reveal that there is still value in continuing to develop the medicine.

The randomised controlled trial (RCT) has been considered the gold-standard in trial design: patients are allocated, at random, to receive a clinical intervention, or a control (which may be a placebo, or the current standard-of-care). RCTs are often 'double-blinded', meaning that

neither the patient nor the physician knows which treatment is being administered. The idea is to reduce bias and assess the drug's efficacy and safety as accurately and fairly as possible.

Regulatory approval

Regulators such as the FDA, the European Medicines Agency (EMA) and, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) assess clinical trial data to determine whether a drug is safe and effective, and can be approved for sale.

In some therapy areas, including oncology and rare, very serious diseases, regulators are increasingly open to clinical trial designs that are less rigorous than RCTs. This is due to the urgency of the unmet need: many patients have no, or few, alternatives. Drugs may be approved on the basis of Phase II trials only, or based on hybrid Phase I/II studies with a very small number of patients. Open-label (non-randomized) trials – wherein both participants and physicians know which treatment is being administered – are also becoming more prevalent, particularly for gene and cell therapies which may involve extracting patients' own cells. In very serious conditions with no existing treatment, it may be unethical to recruit patients into a no-therapy control arm; historic or current clinical data may be used instead.

Regulators approve medicines for a particular indication, which defines the disease(s) or disease sub-sets, and the types of patients for which it may be prescribed. For instance, a drug may be approved for Type 2 diabetes in patients over 50 with a Body Mass Index (BMI) greater than 35. Over time companies can seek approval for wider or other indications based on further data they have developed, which can increase the profitability of the drug.

The regulators do not determine pricing levels or reimbursement.

The BIA has produced a best practice guide for biotech companies on communicating R&D progress to investors. It also guides investors on what information to look for in clinical trial result announcements. The guide can be accessed at: www.bioindustry.org/resource-listing/bia-best-practice-guide-for-communicating-randd-pdf.html

Success rates vary by technology, targeting and therapy area

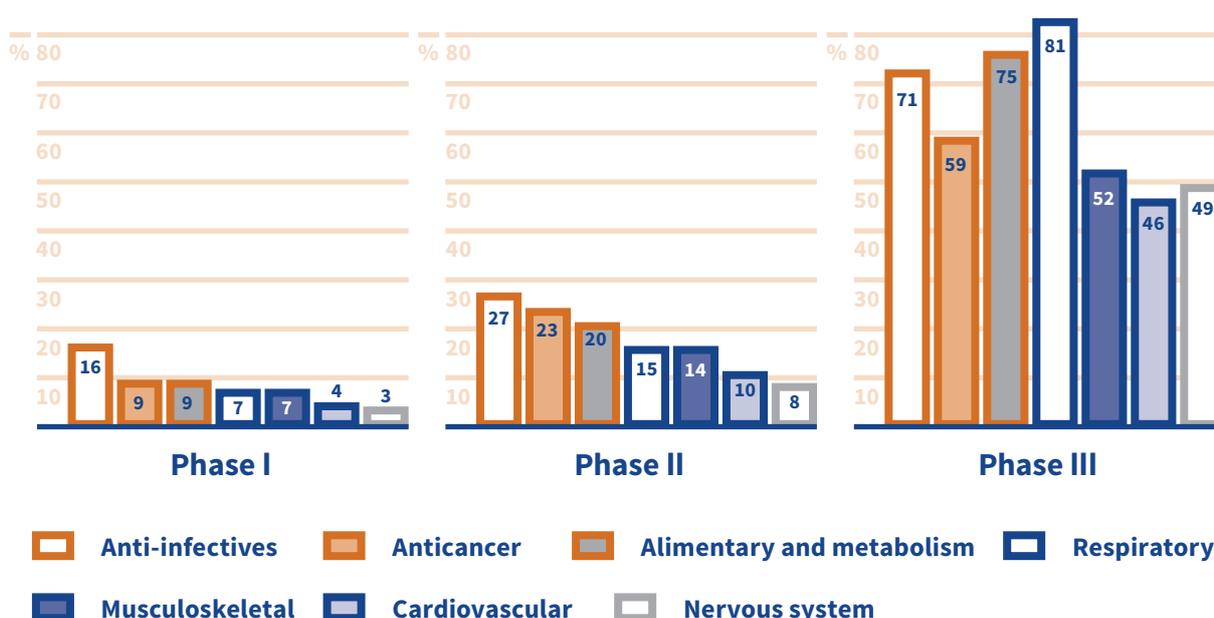
The success rates of medicines R&D are challenging. But they are also very general, aggregating years of data from across multiple programmes. The success or failure of any given candidate is influenced by many variables, which investors should be aware of. These include how targeted a particular drug candidate is, which therapy area or areas it seeks to address, and the company's track record in R&D and in dealing with regulators.

Furthermore, the data above do not capture the significant improvement in late-stage development success rates over the last decade. The likelihood of a Phase III candidate making it to launch was 50% in 2010; today it is almost 60%, according to data from CMR International.²⁰

Some therapy areas enjoy better odds of success

Due to the complexity of disease and our varying levels of understanding of different conditions, some therapy areas enjoy better odds of success than others. For example, drugs for metabolic or respiratory disease are almost 60% more likely to succeed than candidates for heart disease or nervous system disorders, according to 2010–2017 data from CMR.²¹ Anti-cancer drugs sit somewhere in the middle. Drugs for infectious diseases also have an above-average chance of success, in part because laboratory tests can clearly show whether or not they kill the bacteria or virus.

Figure 4: The probability of an experimental medicine reaching the market varies for different therapeutic areas



Source: Centre for Medicines Research (CMR) International, analysis by Helen Dowden and Jamie Munro²²

The chart shows the probability of an experimental medicine reaching market from clinical trial phases I, II and III by therapeutic area from 2010–2017. Only projects for new active substances are included.

Personalised medicines are three times more likely to succeed than conventional drugs

Personalised medicines – designed to treat well-defined patient groups – are three times more likely to succeed than conventional “one-size-fits-all” drugs, according to data from Informa Pharma Intelligence’s *Biomedtracker* and Amplion’s *BiomarkerBase*.²³ These medicines are developed using diagnostics and genetic analysis to identify “biomarkers” which inform patient recruitment into clinical trials. The market for any given personalised medicine is smaller than that of many conventional drugs, but this can be offset by higher success rates, faster development and approval, and higher prices.

Such personalised medicines account for a growing share of FDA drug approvals: 42% in 2018,²⁴ up from 21% just four years earlier, according to the Personalised Medicine Coalition. Hence the number of such medicines in development is steadily rising, too. Over half of all trials initiated in 2018 used some form of genetic-based patient selection, according to Informa’s *Trialtrove*.²⁵ 72% of all breast cancer trials started in 2017 and 2018 used genomics-based tests for patient selection; so did half of non-small cell lung cancer trials.

Orphan medicines and rare disease therapies enjoy faster approval

Many drugs for rare diseases, including targeted medicines addressing rare or advanced cancers, are classified as ‘orphan’ medicines. If they meet certain criteria – including addressing a disease that affects very few patients, and for which there is no alternative treatment – they may enjoy lower development hurdles, faster approval times, longer market exclusivity plus various financial and tax breaks. As we have seen, the cost of developing an orphan drug may, on average, be less than a third of that of a non-orphan.²⁶ This has made orphan drugs a very attractive investment proposition.

Personalised medicines account for a growing share of drug approvals.

The pace of orphan drug approval at the FDA has doubled since 2011.²⁷ Almost half the new drugs approved in 2019 were for rare or orphan diseases. Some drugs may, over time, be approved across several orphan indications, taking their overall target population well above the orphan threshold. One example is Merck’s cancer drug Keytruda, which in 2019 generated \$11 billion in sales across multiple cancer indications.²⁸

Regulators have various mechanisms for accelerating to market treatments addressing serious conditions and which show early evidence of benefit over existing options. The FDA’s ‘Breakthrough Designation’ is one example. Qualifying drugs can expect development times to shorten by an average of three years, and to knock one to two months off review times.²⁹

Regulators in the US and Europe also support new modalities such as cell and gene therapies, which address significant unmet need. They have developed special regulatory pathways for these advanced therapies – many of which are also orphan medicines.

Aanand Venkatramanan

Legal & General

Aanand Venkatramanan is the head of ETF Investment Strategies at Legal & General Investment Management. LGIM runs Exchange Traded Funds across pharmaceuticals and healthcare technology. Their funds invest exclusively in certain publicly-listed companies with free-float adjusted market capitalisations of at least \$200 million, and those whose shares can easily be bought and sold.

Exchange Traded Funds (ETFs) assemble various stocks within a single entity, whose own shares are traded on stock exchanges. They provide investors a proportional stake in all the assets held within the ETF basket. Many ETFs track market or sector benchmarks and aim to match the returns of that benchmark or index.

L&G's Healthcare Breakthrough ETF, launched in 2019, invests in companies building or applying disruptive healthcare technologies across diagnostics, robotics, precision medicine, genomics, data analytics and tele-health. L&G's Pharma Breakthrough ETF, launched in 2018, invests in companies researching, developing and manufacturing orphan drugs. It has out-performed the standard pharmaceuticals benchmark, according to Venkatramanan.

"Liquidity is a primary concern among investors we talk to. Investors want to invest in good products, but things can go wrong, and preferences may change. They want to know that they can always redeem their position without high slippages (e.g. at the price they expect).

"The pace of innovation over the last 15 years means there is a lot more to the healthcare industry than just the Big Pharma companies. We are trying to identify areas with potentially higher growth, like cell and gene therapy, orphan drugs, CRISPR gene editing, robotics, telemedicine and artificial intelligence, that may be of interest to our investors.

"Investors have become more sophisticated. They have access to data like never before, and they are more curious about these areas, even if they come from a non-healthcare background. We try to ensure that they understand our investment rationale. For example, if "we say the orphan drug market is growing twice as fast as other non-orphan segments, because of research incentives and payers' willingness to fund orphan drugs, these arguments are clear.

"Ultimately, though, your strategy has to perform; the proof is in the pudding."

These dynamics, along with the high prices orphan drugs can achieve, explain the rise in the number of speciality medicines in development and on the market. From a biotech investor perspective, they can help reduce cash-flow requirements and compress development timelines, making investment more attractive. This is a trend that is likely to continue.

Biotech financing sources

The R&D process, and so the building of a biotech company, is a highly-capital intensive process. It is primarily financed by successive venture capital rounds and often, but further down the line, public market financings (see Figure 5). A funding round will typically finance a stage of R&D (pre-clinical tests or a clinical trial, for example). Through that stage, a company will build up the evidence (efficacy and safety data, for example) that the product is worthy of progressing to the next stage and is thus able to attract the next round of investment.

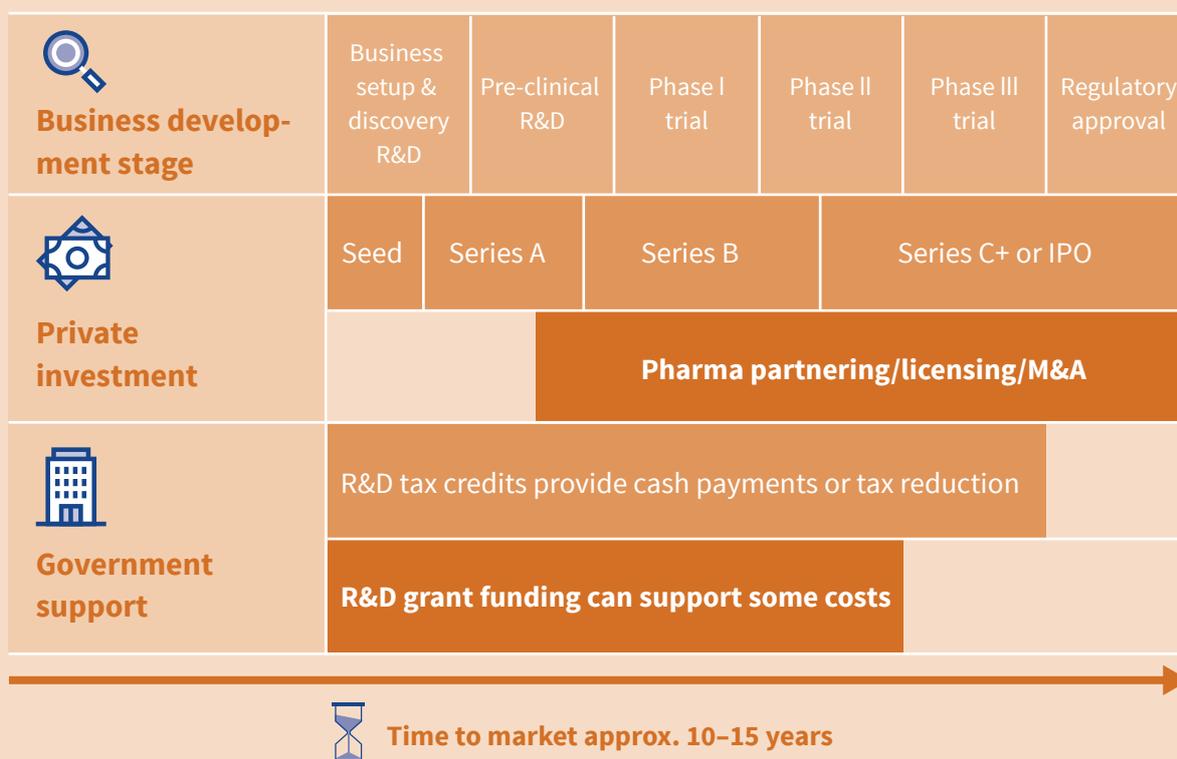
The risk of the investment tends to reduce the further along the pathway it is made (Figure 4) but the amount of capital required at each stage increases. New investors will often join in later rounds, which results in earlier-stage investors being diluted if they cannot also invest to maintain their equity stake. In those circumstances, the intention is that those earlier investors end up with a smaller slice of a larger pie, if the company is successful in the long run.

Traditional equity financing provides the majority of capital a biotech company needs but it is not the only source.

Partnering and licensing, whereby another company – usually a larger pharmaceutical company – provides funding or in-kind support to a biotech's R&D activities in return for rights or a share of the rights to the R&D product, is a common source of finance for biotechs. This capital is usually only available once a product has shown promise and been de-risked, but pharmaceutical companies' hunger for assets means these deals are being made earlier along the R&D pathway. Mergers and acquisitions (M&A) are a similar source of finance, but involve the wholesale transfer of assets.

Biotechs in the UK are also supported by a range of government finance and tax measures that provide additional capital to R&D-intensive companies. Loss-making SMEs can claim cash payments through the R&D tax credit scheme in proportion to the amount they invest in R&D (the face value is 33p for every £1 invested). UK companies can also access a range of government grants to support R&D. Figure 5 shows how these sources of finance may be used at different stages of the R&D pathway and a biotech company's development.

Figure 5: Biotech finance sources along the R&D pathway



Development and investment pathways are simplified and schematized in this figure; private investment stages do not line up neatly with R&D phases.

The medicines market is not like other markets

The market for medicines is different to those in most other sectors. Regulatory approval for a new therapy addressing an unmet need can open up multiple markets across the globe, with companies facing limited or no competition for a set period. Demand for healthcare products is growing and largely non-cyclical. These factors can all impact investor returns.

IP and market exclusivity temporarily reduce competition

New drugs can be protected by both patent exclusivity – 20 years from filing is standard – and market exclusivity. Much of the patent term can be used up during the R&D and regulatory application and approval process, which is why market exclusivity, which may last for 5–10 years after regulatory approval depending on the country, is also offered in most developed countries. It may also include periods of ‘data exclusivity’, during which potential competitors are prevented from using a drug’s safety and efficacy data for their own regulatory approval. This provides drug manufacturers time to recoup their R&D costs and, hopefully, generate a healthy return on that investment.

Once exclusivities have expired, generic and biologic manufacturers may sell copies of a drug much more cheaply, forcing down prices. Various mechanisms exist to extend patent and market exclusivity. Orphan drugs benefit from longer market exclusivity than non-orphans: seven years (rather than five) post-approval in the US, and ten years in the European Union. (Standard EU market exclusivity is two years, but this typically follows eight years' data exclusivity.)

That said, competition from similar but not identical products, and/or payer push back can erode sales well before patents or market exclusivities expire (see below).

Consumers do not pay for drugs; governments or private payers do

Regulatory approval is necessary for commercialisation, but does not guarantee commercial success. In most major markets, consumers do not pay for medicines; governments or health insurers do. These payers must agree to fund or reimburse a given treatment in order for it to reach patients. In theory, manufacturers may set prices freely. In practice they are constrained by how much payers are willing to pay.

In general, pricing and reimbursement decisions are linked to a drug's incremental cost-effectiveness – how much better, and/or safer, it is than existing treatments, taking into account its cost. Drugs addressing diseases where there are no current treatments at all will support higher prices than those in other areas.

Pricing and reimbursement processes vary across (and sometimes within) countries, reflecting different healthcare systems and types of payer. In most European countries, healthcare is tax-payer funded. Some nations have a single payer, such as the UK's National Health Service, or France's *Caisse Primaire d'Assurance Maladie*. Germany has multiple statutory insurance firms, funded by employers and employees. Much of US healthcare is funded by private (commercial) insurance firms, each with different priorities and covered populations.

In national payer systems, once a drug achieves a positive reimbursement decision, all patients across the country should be able to access it. Yet national payers tend to have more negotiating power, given the size of the market they control. This can lead to lower prices and/or more restricted access – especially as payer budgets are squeezed by the demands of an ageing population.

In the US, drug companies must negotiate with multiple payers. Published or “list” prices in the US tend to be significantly higher than those in Europe; yet US payers negotiate often large (and confidential) rebates and actual prices paid may be well beneath list price. US payers can also restrict how many patients can access a given product.

Most payers are willing to cover new treatments that address serious unmet needs and demonstrate clear added-benefit relative to existing options. Increasingly engaged patients and patient associations can also exert pressure on payers to provide access to important therapies. Drugs for rare diseases command higher prices than mass-market drugs, because companies will have fewer sales to recoup R&D investment costs and low patient numbers limit the overall budget impact for any given payer or health system.

The revenues achieved by a given drug ultimately depend on the size of the unmet need (how many patients need the treatment), pricing and reimbursement (how many patients can access the treatment), and the competition – which includes how many similar treatments are available, and their relative cost.

The best-trodden routes to realising returns: licensing, M&A and IPO

There are many ways for biotech companies and their investors to achieve returns before a product actually reaches the market. Indeed, few biotech companies take a product from discovery to commercialisation on their own.

Licensing and M&A can generate early returns on investment

Most biotech companies license out their assets to larger pharmaceutical companies, or are acquired, before regulatory approval. The pharmaceutical industry urgently needs to access new drugs as many of their older medicines face generic competition and pricing pressure. They source these from biotech. Pharmaceutical companies have the commercial and marketing expertise and infrastructure that most biotech companies lack. Indeed, their ability to take an approved drug out of the laboratory and into widespread commercial adoption is one of the key distinctions between biotech and large pharmaceutical companies.

Over half of all FDA approvals over the last four years have either originated within, or been developed by, biotechs. So large companies are falling over themselves to access the most promising assets, resulting in high-value licensing deals and acquisitions.

The combined value of acquisitions is up by almost 70% globally since 2009, according to Informa's *Biomedtracker* database.³⁰ Acquisitions involving UK companies were worth almost five times as much in 2019 than in 2009.

The pharmaceutical industry urgently needs to access new drugs, which they source from biotech.

Licensing deals usually involve an up-front payment, or licensing fee, and milestone payments due if and when a experimental drug progresses through development and approval. This creates revenue for biotech companies. Sales royalties may also feature; in rare cases the licensor (who developed the drug) may maintain some commercial rights, for instance in a home market.

The sweet spot for licensing deals has typically been toward the end of Phase II testing – when there is “proof of concept”, or some evidence that the drug works in humans. Licensing at this stage means the larger partner decides how the final, and most costly Phase III trials are run.

But competition (and expedited development pathways in some indications) means that large pharmaceutical companies are licensing or buying sooner, often well before Phase II is complete, and, before the pandemic, they were paying richly, even for these less mature assets. Licensing deals between large companies and biotechs in discovery stage and Phase I grew 10% and 20%, respectively, from 2017 to 2018.³¹ Median M&A premiums paid for research-stage biotechs reached a five-year high during 2019, and average up-front payments in licensing deals also increased. The median up front for pre-clinical assets rose from \$12 million in 2018 to \$20 million in 2019, according to Evaluate.³²

The coronavirus pandemic dampened those numbers in the early part of 2020, as lock-down constraints and economic uncertainty delayed deals, re-jiggered some company valuations, and as urgency grew among some sellers (creating a buyers' market). But it did not change multinational pharmaceutical companies' fundamental need for biotech assets. This explains why dealmaking continued through the early months of the crisis, and why valuations mostly held up.

Deals carried out earlier on in a biotech's development can reduce re-financing and dilution risk for the company and investors, as they may no longer need to issue new equity to fund R&D. Some venture capitalists are also designing 'build-to-buy' biotechs specifically to attract a pharmaceutical partner early on.

If a biotech is acquired outright – which can happen when multiple bidders are after the same asset, and/or when biotech companies are unwilling to sell a programme in isolation – investors enjoy healthy returns, faster.

The growth in treatments for very niche conditions is enabling some well-funded biotechs to market and sell their own products. This creates more opportunities for biotech investors. For now, though, such 'fully-integrated' biotechs remain the exception. Large pharmaceutical companies are just as interested in these specialist assets, given the accompanying development, regulatory and commercial tailwinds.

IPOs provide access to fresh capital for companies and exits for some investors

A public listing can open up larger pools of capital to support later-stage development within a biotech. It can also provide an exit opportunity for some investors.

Europe lacks a single, shared exchange for growth companies. European biotechs may list on a local market such as AIM in the UK, Amsterdam-based EuroNext or the Stockholm Stock Exchange. These typically have less onerous and expensive listing requirements than American exchanges.

Increasingly, however, European companies are choosing to list exclusively, or additionally, in the US. In 2019, all but one of the top eight European biotech IPOs were on Nasdaq. The reasons are clear: Nasdaq biotechnology IPOs raise three times more than European IPOs, on average, according to analysis by McKinsey.³³ There are many more investors in the US, including specialist investors, offering access to a deeper combined capital pool, greater exposure and more extensive analyst coverage.

Chris Hollowood

Syncona

Chris Hollowood is the chief investment officer at Syncona, a UK-based investor and company-builder, with a strong focus on cell and gene therapy. Syncona is structured as a closed-ended trust, listed on the London Stock Exchange. The business aims to found, build and fund sustainable global leaders in life science with a vision to create a portfolio of 15–20 companies focused on delivering transformational treatments to patients in truly innovative areas of healthcare. Syncona takes a long-term view and has a capital base that is used to back its companies. The structure offers Syncona the flexibility to invest the sums that its companies require, at the time they need it, without the constraints of fund timeframes or market conditions.

“The UK is a world-leader in cell and gene therapy, with a critical mass of academic research embedded within the university and hospital environment. Cell and gene therapies are not just reducing the impact of disease, they are curing diseases. We draw a parallel with small molecules and antibodies, both of which powered the industry for multiple decades. Cell and gene therapies will be the same. It is a great story.

“So, at the individual company level, is that of gene-therapy play Nightstar Therapeutics. Syncona co-founded the company in 2013, with an initial investment of £16 million. In 2017, Nightstar listed on the US Nasdaq exchange. In early 2019, the company was acquired by Biogen for \$877 million, marking the third-biggest biotech exit in UK biotech history. We made a 4.5x return on our overall £56.4 million investment in just over five years and 9.5x on the Series A investment.

“Timeframes used to be longer: early investors in UK biotech pioneers Celltech and Cambridge Antibody Technology had to wait over 20 years for their returns. Celltech was acquired by UCB in 2004 for £1.5 billion; CAT was acquired by AstraZeneca in 2006 for £702 million.

“There is a strong case to be made for UK and European companies’ accessing Nasdaq. In order to build global leaders here in the UK, we need to have access to capital at the same cost as our competitors. There is no shame in a US listing. These companies are still UK PLCs that pay taxes and employ people in the UK.”

Since 2012, almost a third of European biotech IPOs have been filed in the US, and almost all (98%) of follow-on finance raised by European biotechs has been on US, not European, exchanges, according to McKinsey.³⁴ Several UK companies have listed directly on Nasdaq in recent years, without going public locally. These include Bicycle Therapeutics, which raised \$60 million in 2019 for its peptide-based cancer therapies, and gene-therapy player Orchard Therapeutics, which raised \$225 million in 2018, two years after spinning out of University College London. Compatriot Autolus, developing next-generation CAR-T therapies for cancer, achieved \$160 million in its June 2018 debut. Gene-therapy focused Nightstar Therapeutics raised almost \$80 million in 2017 and was acquired little more than a year later by US-based Biogen for ten times that.

Most of these companies remain UK-headquartered, and continue to do R&D in the UK. They illustrate UK companies' globally competitive standing and the accelerated return timelines that investors can achieve.

How to value a biotech

Most biotech companies are loss-making for many years, with no or very occasional earnings (such as one-off milestone payments from a partner). This means traditional metrics such as EBITDA or price-to-earnings ratios (for listed companies) are irrelevant. Service-focused companies with regular revenue may be more easily valued using traditional techniques.

Valuing drug discovery biotechs is difficult. Inevitably, this complex exercise is as much a subjective assessment of risk as it is a quantitative assessment of commercial opportunity (see Box 7). It involves putting a future value on the pipeline, which may include one or several R&D assets. Each may vary by indication, degree of novelty, and stage of development. Forecasting the timing and size of future sales must take into account market size, competition and pricing dynamics, as well as the likelihood of regulatory approval.

In the end, valuation – and a decision to invest – may combine different methods. It may boil down to some key questions including whether the assets have the potential to make a meaningful difference to patients, whether the company leads its field, the size of the market and the quality of the team.

Box 7: Risk-adjusted NPV

Biotech investors most commonly use the ‘risk adjusted net-present value’ method. This involves projecting future cash flows for an asset, assessing the probabilities of various different scenarios, and then estimating the present value of these probability-weighted future cash flows for a given candidate. There is considerable uncertainty involved.

Future cash flows for a given asset will depend on whether and how fast the drug is approved, in which markets, for how many patients, and at what price. It will also vary according to whether the biotech company is marketing the drug itself, and therefore booking all the sales, or whether a larger partner is commercialising the drug, perhaps paying royalties to the biotech. Average gross margins for biotech and pharma products are between 68–70%, according to a Stern School of Business study, but the cost of sales for any company will depend on the indication and competitive landscape.³⁵

These cash flow projections are then probability-weighted. This brings in the previously-discussed success rates for the various stages of R&D and approval, as well as other less tangible factors including the company’s management and track record. A drug’s probability of success will vary considerably depending on what stage of trials it is in; this explains the prominence given to the successful transition from one phase to another, since this can substantially change the perceived value of a drug candidate. Yet there is no single, accepted dataset for these phase-linked success probabilities. Investors’ views of a particular asset’s chances may differ – influenced, for example, by therapy or technology area, commercial

considerations, and/or the performance of similar drugs. This alone can generate significant volatility in the valuations of individual biotech companies.

These probability-weighted future cash flows are then discounted to generate a net-present value. There is no standard discount rate, since there is no standard biotech company. But in general, the closer the biotech is to having an approved product, the lower the discount rate used.

Such analyses may be carried out for each asset within a biotech company, generating a series of NPVs which are constantly adjusted as new evidence emerges. Within a given portfolio, the probability of success of one candidate may be linked to that of another if it uses the same underlying technology.

Benchmarking can be used, but is not often appropriate since each biotech tends to combine a unique set of assets, and follow its own trajectory (though comparisons are made to similar groups or transactions).

In short, biotech valuation is not a simple, uniform exercise. Many institutional investors will use in-house or external specialists to assess clinical trial progress and to quantify commercial potential. Investors who do not have access to that internal resource will usually look to equity research from investment banks and stockbrokers as a substitute. For those investors who still feel uncomfortable with their lack of specialist knowledge, the use of collective investment vehicles managed by specialist investors has become an increasingly popular alternative.

The biotech opportunity on your doorstep

Flourishing science, diverse business models plus hungry, deep-pocketed buyers are playing in biotech investors' favour. So, in Europe, are attractive company valuations and increasing access to dynamic US public markets. In this chapter we take a look at why investors should be taking more interest in UK biotech.

Biotech delivers competitive returns

The biotech sector has delivered significant rewards to investors, both public and private. It tends to favour long-term investors.

Healthcare-focused private (venture) funds in the US have generated internal rates of return (IRR) of between 20% and 60% since 2009, most years either exceeding or in line with the performance of funds in financial services, software or IT according to 2019 data from Cambridge Associates.³⁶ Within that broader 'healthcare' segment, biotechnology/drug R&D outperformed pharmaceuticals, healthcare services and medical devices most years since 2009, generating an astounding 59% IRR in 2012, and over 95% in 2013.

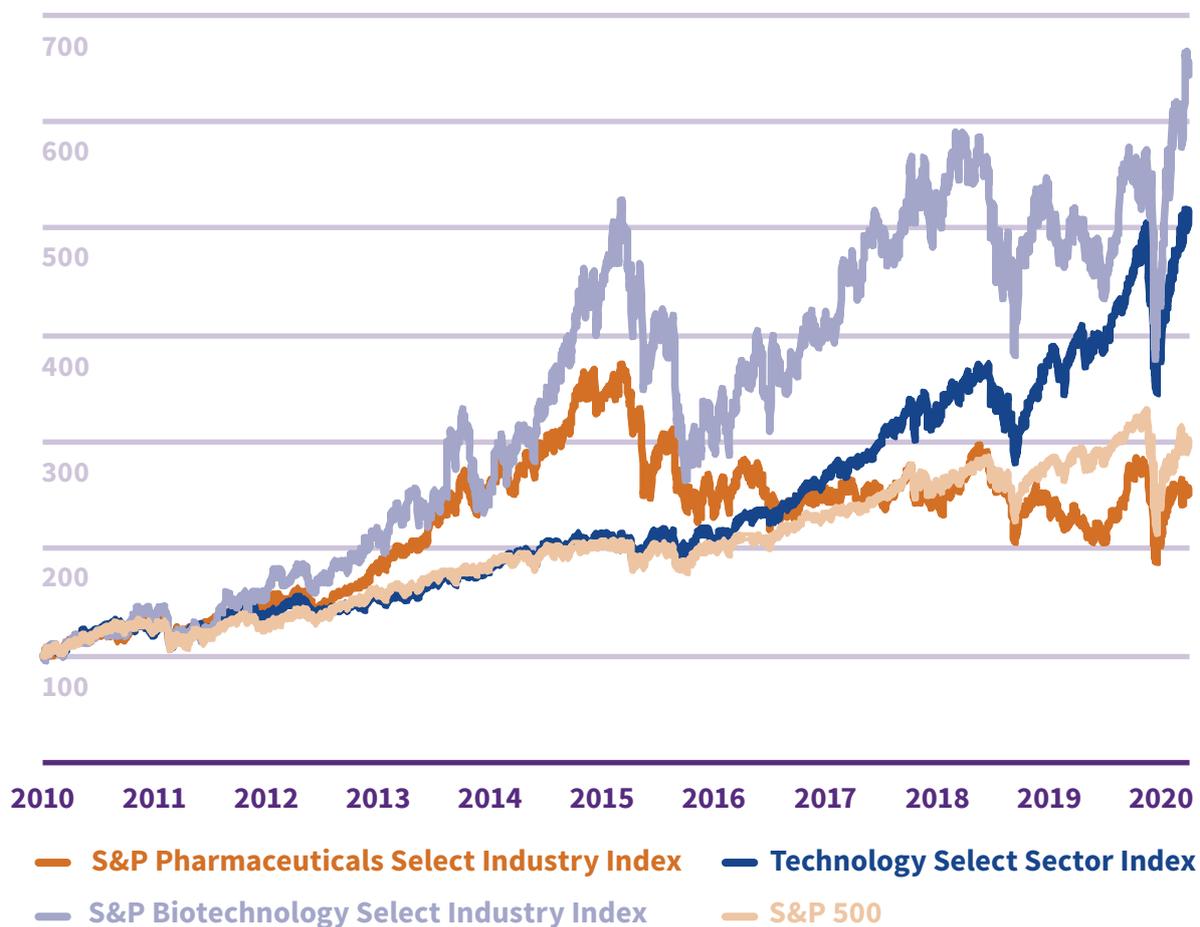
Data on the returns of UK biotech venture capital is less readily available. Data from the UK's Association of Investment Companies (AIC), however, ranks Biotechnology & Healthcare as the top performing investment company sector of the last decade.³⁷ It produced an impressive 491% return from 2010 to 2019, compared to 198% for the average investment company over the same period. Investment companies – also called investment trusts – invest in private and smaller public companies, but are not limited to the UK.

Biotechnology & Healthcare is the top performing investment company sector of the last decade.

Strong long-term performance can also be found on the public markets. Annual returns from the US Standard and Poor Biotechnology Select Industry Index over ten years to the start of 2020 surpassed 17%, out-pacing those of the broader S&P 500 and of the Pharmaceuticals Select Industry Index (Figure 6). Shorter term timeframes (3–5 years) haven't been so competitive.

The sector also tends to be counter-cyclical, meaning it can do better when other sectors are not faring so well. Public UK biotechs have demonstrated this during the COVID-19 economic shock. Many sub-sectors of UK biotech have consistently out-performed the wider FTSE All-Share index over the last two years, but this positive trend has become much more pronounced since COVID-19 began disrupting markets (Figure 7).

Figure 6: S&P Biotech, pharma, tech and 500 10-year share price performance



Source: S&P Dow Jones Indices³⁸ (As of 1 July 2020)

Figure 7: Performance heatmap: unweighted UK quoted biotech vs FTSE All-Share Index

Performance relative to FTSE All Share (%)	As of 1 July 2020			vs	As at 31 December 2019		
	1 year	2 year	5 year		1 year	2 year	5 year
Small molecule bio therapeutics	+95.1	+51.3	+32.5	vs	+8.3	-17.5	-36.1
Cell and gene therapies	+99.5	+106.3	+66.9	vs	+28.6	+33.5	-0.0
Research tools and data	+82.5	+71.6	+49.2	vs	+4.1	-2.3	-23.2
Diagnostics	+136.4	+139.2	+132.4	vs	+7.0	+5.1	-7.1
Medical devices	+29.1	+31.1	+65.3	vs	+9.4	+11.5	+41.6
Commercialisation and investment vehicles	+36.6	+36.5	+57.3	vs	+2.4	+2.5	+15.8
Covide-19 specific	+255.0	+294.3	+162.4	vs	+32.7	+48.3	-12.7

Source: Radnor analysis of FactSet

This heatmap shows the 1, 2 and 5 year relative performance of each sub sector within biotech (darker green = outperformance, darker purple = underperformance) compared to the FTSE All-Share Index. The biotech element is assessed as an unweighted index due to the dominance of one or two larger companies.

Global investors recognise the European biotech opportunity

Europe and the UK have a world-class science base. One third of the top 50 life sciences universities is in Europe, and four of the world's top ten universities are in the UK. British inventions underpin some of the most successful pharmaceutical products and technologies in the world. Europe spawned the first approved gene therapies and continues to be a hot bed of medical innovation, with the UK at its leading edge. The region is also home to an expanding pool of entrepreneurial and management talent.

Europe benefits from more international investors and larger funds

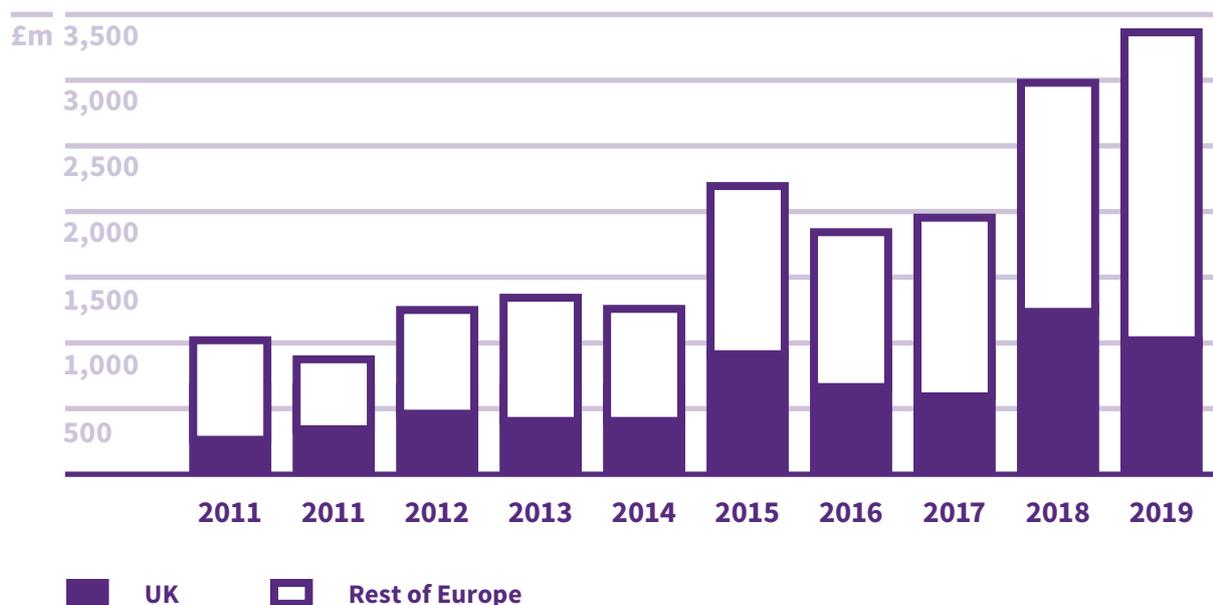
The amount of venture capital available to European biotechs has more than doubled in less than a decade, with UK companies now accounting for 29% of the total raised (Figure 8).³⁹

Europe's flourishing science base is attracting a growing range of private investors from across the globe. The US accounted for almost a fifth of investments in early-stage European biotechs between 2012 and 2018, compared to just over 10% in the 2005–11 period.⁴⁰ China accounted for 3.3% in 2012–18, more than six times its share in the prior five years.

Furthermore, European private investors, like their US counterparts, are raising ever-larger funds. Average fund size has doubled over the last seven years, and the range of funds has widened.⁴¹ Larger funds mean investors can support promising projects and companies for longer.

Family offices have also become more prominent in biotechnology over the last few years, as wealthy individuals seek impact investments, alongside exciting financial returns. Angel investors and networks are growing in sophistication. Pharmaceutical companies' corporate venture arms increasingly support early-stage biotechs, often investing alongside traditional VCs or as partners. Healthcare-focused private equity players – traditionally focused on larger, revenue-generating businesses – are also taking an interest in biotech, given its potential to offer far higher returns than most conventional healthcare companies.

Figure 8: Private financing for European biotechs



Source: BIA analysis of Pitchbook

Further, the COVID-19 pandemic has not dampened the interest of non-traditional investors in biotech; indeed, it may well prove to have strengthened it. During the early part of the crisis, amid highly volatile public markets, investors flocked to perceived safe-haven sectors including biotechnology. They were attracted to a sector whose products address meaningful, long-term challenges that now sit even higher on governments' and the public's priority-list.

In short, Europe is freeing itself from traditional constraints, which have in the past included a relatively narrow, risk-averse investor base, a shortage of early-stage capital, and the absence of a Europe-wide growth exchange.

Europe offers good-value investments

International investors are drawn to Europe's strong science, dynamic company-creation and attractive valuations. Ahead of the COVID-19 shock, pre-money biotech valuations were significantly higher in the US – sometimes up to three times higher, according to McKinsey.⁴² As the pandemic showed, however, these differences can fluctuate widely, and depend on the particular company, therapeutic class and the level of unmet need, as well as market sentiment in both locations.

Alongside increasingly sophisticated and international private investors, Europe also offers lower company start-up and running costs than the US. A European biotech's running costs may be just 60% of those of a US competitor. This is largely because of higher average US salaries for life science professionals.⁴³ Attracting and retaining talent is also easier in Europe than in the top US biotech clusters, as there is a lower density of biotech start-ups seeking to poach the best scientists.

Europe and the UK have a high proportion of service companies supporting drug discovery, rather than developing medicines themselves. A quarter of Europe's biotechs are service providers (including diagnostics, contract research or manufacturing organisations), versus just 15% in the US. These companies offer exposure to the drug development market with lower-risk investment opportunities, often with existing revenues and demonstrable long-term growth. Investors in such companies can enjoy faster, and potentially less risky returns; return multiples are also likely to be lower, however.

The UK is home to some pioneering investment vehicles

Houman Ashrafian

SV Health Investors

Houman Ashrafian is managing partner, biotechnology, at SV Health Investors, a healthcare and life sciences VC and growth equity firm. He explains why he invests in biotech, and why the Dementia Discovery Fund is the first of its kind.

"I invest in biotech because new drugs have a significant impact on patients, as well as offering investors significant upside. In the UK, we have world-class science, which remains relatively un-tapped. We have better [cheaper] company valuations than in the US, and it's cheaper to run companies here. A newly-qualified PhD in

Europe costs almost half what it does in the US. Recruitment and retention is not as challenging, either.

“The UK is also really strong on big, ambitious, multi-disciplinary initiatives, like Genomics England, HGI UK and the UK BioBank. Even though the UK is not a huge market commercially, relative to the US, everyone here has an NHS number. We are a larger, more diverse population than those in Finland or Iceland [which also have country-wide health data]. Access to the NHS for clinical trials is getting faster and easier.

“In short, the UK is the place to do precision medicine trials; we have unparalleled data sources and sophisticated investors.

“The UK is also home to some pioneering investment vehicles, like the Dementia Discovery Fund. This is the first and largest venture capital fund focused on a single disease area. The DDF was instigated by the UK Government, and in 2018 raised £250 million – twice its initial target – from UK and US charities and industry. The goal is to diversify the range of targets and approaches being tested for all forms of dementia, including Alzheimer’s disease, and to better understand this increasingly prevalent, and woefully under-served condition. The 15-year DDF is managed by SV and aims to make a profit for its backers, but is also driven by a strong societal need.”

The UK is the leading European biotech cluster

The UK is the leading biotech cluster in Europe and is third globally behind San Francisco and Boston.

The UK generates three times as many start-ups as its European counterparts, according to McKinsey;⁴⁴ over a third of all new biotechs created in Europe since the start of 2012 have been in the UK. There are now over 4,600 small and mid-sized companies using biotechnology to solve health-related problems⁴⁵ and investment in private UK biotech companies has increased by over 400% since 2012.⁴⁶ UK companies attracted a quarter of Europe’s private biotech financing in 2019, and topped the charts on the size of rounds, too.⁴⁷

This thriving sector is built upon the most productive science base in the G7 group of developed countries.⁴⁸ The UK has four of the top ten global universities for life sciences and produces 18% of the world’s top life sciences publications.⁴⁹

Katerina Sanchez-Schilling

NCL Technology Ventures

There are innovation clusters across the UK

Katerina Sanchez-Schilling is an investment manager at early-stage venture capitalist firm NCL Technology Ventures. NCL invests primarily in UK-based therapeutics, digital health and medical technology groups, typically at the seed-stage or in Series A, though their remit is geography agnostic.

“One reason for our heavy focus on UK-based investment opportunities is the country’s fantastic network of universities and world-class research facilities. Another is the strong government support for life sciences start-ups and entrepreneurs including via R&D tax credits. The UK’s multi-disciplinary talent base is also a huge draw – as are the country’s multiple, relatively tightly-packed innovation clusters. Those clusters are not limited to the “golden triangle” of London, Oxford and Cambridge; they include increasingly dynamic hubs in Scotland and in the North of England. Leeds, for example, is enjoying a renaissance in start-ups and new businesses.

“These factors have helped foster a wide network of angel investors in the UK – well above 15,000 in total, according to the British Business Bank. This is more than in most other European countries, which tend to be more risk averse. Many of these individuals are passionate about the sector and want to help bring about technologies and therapies that can have a positive impact. They provide start-ups and entrepreneurs with patient, early-stage capital (typically between £10,000 and £500,000, with investment horizons of 6–7 years or more) as well as expertise, often drawing on their own experiences in biopharma, medicine or healthcare more broadly. This in turn helps create a strong pool of companies for VCs, both domestic and from abroad. Many of these experts have stepped up during the current crisis to provide guidance and support to young companies, which I take great comfort in.”

UK biotech enjoys long-term government support

UK governments of all colours have offered a supportive policy environment for life-sciences for the past two decades. Prime Minister Boris Johnson has been more vocal than any past leader on the importance of the life sciences, and specifically the biotechnology industry. The Conservative manifesto declares an ambition to expand the UK’s position as a global life sciences hub and the COVID-19 crisis appears to only have strengthened that resolve.

The UK Government supports the life sciences sector through a range of vehicles and policies, including grants for early-stage R&D, access to equipment and facilities, tax incentives for investment, corner-stoning VC funds, and promoting the sector through published strategies and trade missions. Together, these initiatives have helped make the UK one of the most attractive, and cost-effective, locations in the world to conduct life sciences R&D.

The Government invested £5.1 billion in life sciences R&D between 2016 and 2018.⁵⁰ Much of this supports a world-class science base in the UK’s universities and public

research institutes. This basic research provides the critical foundations for investors and industry to build upon and translate into actual products. Asset- or technology-linked IP is licensed from universities (in exchange for fees) and companies are created around those assets, attracting seed and venture funding for further development. Charities are another important source of early-stage R&D funding; they invested £1.9 billion in medical research in 2019.⁵¹

The Government-funded UK innovation agency, Innovate UK, provides grants directly to companies to support R&D. Between 2016 and 2018 £540 million was awarded to small and mid-sized life sciences companies.⁵²

The Government also invests in facilities and infrastructure that SMEs could not afford alone. This includes support for major data-collection initiatives such as the UK Biobank (see Box 8) and investment in centres of excellence around new technologies. The Cell and Gene Therapy Catapult, for example, was established in 2012 at Guy's Hospital in London to provide SMEs access to clinical trial, technical, manufacturing and market access expertise across cell and gene therapy.

The UK tax environment is one of the best in the world for innovative companies. R&D tax credits provide cash payments or tax relief to companies that invest in R&D. A loss-making biotech will receive 33p back from the Government for every £1 it invests in R&D. This makes the UK the 5th most generous tax credit system in the world.⁵³ Once a company becomes profitable, the Patent Box provides a lower corporation tax bill on all profits derived from patented technologies.

Investors in innovative UK companies also enjoy a range of tax reliefs. The Enterprise Investment Scheme (EIS) and Venture Capital Trusts (VCTs) offer attractive income tax relief (worth 30% of the cost of investment) and capital gains exemption on investments in small, unquoted companies or those listed on London's AIM.

In 2016, the Government launched the 'Patient Capital Review', which investigated the state of long-term or 'patient' investment in the UK. It concluded that more could be done to encourage and facilitate such investment, both among retail and institutional investors. This resulted in the British Business Bank launching a new £2.5 billion fund called British Patient Capital, which will invest in UK VC funds to leverage a further £5 billion investment in small and growing UK businesses over the next decade.⁵⁴ The Government has since committed to a further £200m ring-fenced for life sciences. Investors in private UK biotech can therefore benefit from Government money investing alongside them, sharing risk and potentially increasing the chance of positive returns. The Government will also work with defined contribution pension schemes to encourage greater investment by such institutions in venture capital assets. As part of this work, the British Business Bank has published analysis showing that pension savers could increase their retirement savings by 7–12% by investing a small proportion of their portfolio in venture capital.⁵⁵

The Government's support for the sector – encapsulated in the Life Sciences Industrial Strategy and two related Sector Deals – should help support continued growth and investor returns as new medicines are developed.

Box 8: UK health data initiatives give the sector a competitive edge

The UK's nationwide health system offers researchers an unparalleled data source. It holds health-related information from almost all individuals across a large, diverse population. This data is becoming better integrated and more accessible, thanks to government-funded initiatives designed to enhance innovation and drive meaningful health solutions.

This data gives the UK a significant competitive edge over other regions. Health data pools in many markets are fragmented, locked within individual health systems or insurance firms. As drug development – and delivery – becomes more personalised, the value of health-related data is skyrocketing.

The NHS also offers drug developers a unique resource for clinical trials. The Medicines Company, a US group now owned by Swiss pharmaceuticals giant Novartis, came to the UK to recruit the vast majority of patients in its 15,000-strong Phase III study of cholesterol-lowering injection inclisiran. Aggregated hospital discharge data pulled together by NHS Digital, the NHS' information and technology partner, enabled suitable patients to be rapidly and accurately identified. Trial sites were set up five times faster than is typical, according to a trial coordinator.

Key UK health data-focused initiatives include:

NHS Digital

The NHS' information and technology partner, supporting integrated clinical research within the NHS and greater access to data to drive innovation.

Digital Innovation Hubs

These link regional NHS data centers, covering regions of 3–5 million people in total, to allow the data to be analysed and accessed for research.

Health Data Research UK (The national institute for health data science) Working to enhance appropriate access to health data for researchers and innovators.

UK BioBank

Non-profit initiative to collect a wide range of health data, including genomic and behavioural information, from half a million individuals. The resource – enriched by longitudinal data, as participants agree to be followed through their lives – is being linked to electronic health records to provide a fuller picture of disease onset, prevalence and progression. UK BioBank is attracting academic and industry researchers from across the globe

Genomics England

Government-funded organisation that has sequenced more than 100,000 genomes from patients with common cancers or rare diseases, helping uncover causes, treatments and diagnostics. Genomic data is being linked to broader medical data (e.g. hospital visits, imaging and diagnostics) and other therapy-area specific datasets.

Daniel Mahony

Polar Capital

Daniel Mahony set up the healthcare team at investment management company Polar Capital in 2007, and is currently Co-Head of Healthcare. Polar's health-focused vehicles include Polar Biotechnology, a £400 million open-ended fund invested in biotechnology and life sciences tools and services, and the Polar Capital Global Healthcare Trust, which invests in healthcare equipment groups, pharmaceutical companies and listed biotechnology companies.

"I'm obsessed by digital. Digital technology is transforming how healthcare is managed, delivered and paid for. Its advantages were particularly evident during the COVID-19 outbreak, when many doctor-patient consultations were carried out online or using telemedicine.

"We have a great opportunity in the UK to be a leader in this area, thanks to our NHS data, disease registries and many other data-focused initiatives across the UK. This data can support drug R&D, for instance through accelerated trial recruitment. But it can also be used to design and create optimal care pathways, and care delivery, for patients across the globe.

"Digital is also helping make the products of biotechnology more visible to consumers in their daily lives, driving awareness and interest. Whether it is apps that help book doctors' appointments, to direct-to-consumer genetic testing services, or increasingly sophisticated, wearable sensor-based diagnostics such as continuous glucose monitors for diabetic patients, the range of healthcare products is increasing.

"Innovation is accelerating, in both the scientific and digital realms. The UK can lead the world in digitalizing healthcare. We just need to get on and do it. Initiatives like the NHS clinical entrepreneur training programme which encourages clinicians to be more entrepreneurial and provides digital health skills, are a great start."

Genomics and health data provide powerful weapons to combat pandemics

Julia Wilson

Wellcome Sanger
Institute

Julia Wilson is Associate Director at the Wellcome Sanger Institute, based just outside Cambridge, UK. The institute played a leading role in the sequencing of the Human Genome in 2001. Now it is deploying its genomics-focused expertise and infrastructure in the battle against COVID-19.

“A great science base and long-term investment in the UK genomics infrastructure gave us the strong foundations we needed to rapidly engage in helping understand and mitigate the impact of COVID-19. The Wellcome Sanger Institute, alongside more than 12 academic partners, the NHS and the UK’s four public health agencies, pulled together with incredible speed and agility to create the COVID-19 Genomics UK Consortium. They were supported by £20 million from the Department of Health and the Wellcome Trust.”

“As of the end of May 2020, the Consortium had sequenced over 20,000 viral genomes from patient samples collected from hospitals and testing centres nationwide – the largest number of COVID-19 genomes sequenced by any single country. These genomes – shared openly with the wider academic community – enable scientists to identify new lineages (small changes to viral genomes) that may emerge, helping monitor and track the virus’ transmission into and across the country.”

“This provides powerful information with which to combat the virus’ effects. For example, data tracking virus spread at a local level could be used, in combination with other health and population data, to monitor the effects of re-opening schools. The emergence of any particularly virulent sub-strains could be flagged and appropriate local action taken. Already, the data indicates that as of May, several months into lockdown, transmission patterns were mostly local rather than imported from abroad, and that all viral lineages share a common ancestor from China.”

“Other Sanger Institute scientists are working to understand the virus itself and how it enters the body. One group has identified particular types of cells in the nose that are the most likely entry points for COVID-19. Another is looking at whether and how the virus can pass from pregnant mothers to their unborn babies. Both groups tap into the institute’s existing Human Cell Atlas datasets, which contain detailed genomic and molecular information about different cell types in the body.”

“The UK’s strengths across genomics and health data provide powerful weapons with which to combat this and future pandemics, and underscore the value of investing in science and data collection.”

Ways to invest in biotech

Biotechnology has delivered strong investor returns over the last decade, in both the private and public spheres. There is a widening choice of ways to invest, from stock-picking listed companies to spreading risk via private or public investment vehicles.

Multiple opportunities to diversify and spread risk

The sector's diversity allows fund managers and individual investors to build portfolios that are spread across geography, therapy area, maturity and modality (gene therapy, small molecule etc.).

Investors can select product-focused companies alongside tools or service-based groups, and include digital health or data analytics companies too. Health-focused biotechs may be combined with groups focused on the agricultural and/or industrial sectors. The London Stock Exchange has over 75 companies classed as "biotechnology", which span all these subsectors and business models.

Investing directly into companies, including those listed on AIM, is generally for the professional and sophisticated investor. But specialist knowledge of companies and individual technologies is not necessary in order to gain risk-adjusted exposure to biotech. There are a range of collective investment vehicles on the market that provide access to exciting companies and technologies, with risk-levels and time-frames to suit different investors' requirements.

The following section provides a high-level overview of investment vehicles. Professional advice should be sought to identify the most appropriate vehicle for your requirements.

Collective investment vehicles provide a portfolio of biotech companies, spreading investment risk.

Collective investment vehicles provide access to a mix of companies

Collective investment vehicles, including closed-ended investment trusts and open-ended funds, provide access to a portfolio of biotech and pharmaceutical companies, spreading investment risk. There are various products on the market, offering exposure to a range of public and private healthcare companies. Some are accessible to all investors; others, such as private equity and venture capital funds, are for professional investors only, or accessible only via intermediaries.

Several of the retail funds (available to all investors) have a broad healthcare focus and are often heavy on established pharmaceutical companies. Exposure to biotech, especially smaller European biotech, is limited or non-existent in such vehicles. Investment trusts may track a global healthcare index (such as FTSE or S&P) which includes pharmaceuticals and large-cap biotechnology stocks. These may be very US-focused.

Specialist healthcare funds select a range of pharmaceutical, devices, biotechnology and sometimes health insurance and healthcare provision company stocks. These may provide a degree of exposure to European biotech but generally the broader the fund, the less likely it is to include smaller and scaling biotech companies. There are some biotechnology-focused funds which invest exclusively, or almost exclusively, in European or global biotechnology stocks. There is likely to be higher volatility and risk in such portfolios, but with it comes the potential for greater returns.

Widely accessible vehicles

The following types of UK investment vehicles are available to a broad range of investors, and provide exposure to public or private companies, or a mix of both.

Unit Trusts

Unit trusts are the most common investment vehicle in the UK market. They are run by fund managers who decide which individual company stocks to include in the trust. The open ended nature of unit trusts means that when investors want to put in new money, new units are issued and sold to them; conversely, when investors seek to redeem their funds, the units are sold back to the fund manager. Units are valued by dividing the value of the underlying investments held in the vehicle by the number of units in issue, so the unit value is tied to that of the underlying assets. The number of units – and the size of the fund – grows or shrinks in line with investor demand.

The popularity of open-ended vehicles stems from their inherent flexibility to grow, or shrink, the size of the fund in response to investor demand. As a rule of thumb, open ended vehicles are better suited for more liquid, mainstream investments, however. They can be exposed to liquidity risk if illiquid assets need to be sold in order to satisfy investor redemptions. This was seen in the 2019 closure of Neil Woodford's funds, which were unable to pay back investors.

UK biotech offers a widening choice for investors

Andy Richards CBE

Serial entrepreneur

Andy Richards is a UK-based serial entrepreneur and investor, chairman and/or advisor to private and listed biotech companies, technology transfer organizations and venture capitalists. He was a founder and executive director of Chiroscience, one of the first UK biotech companies. Andy has witnessed first-hand the sector's evolution to include an increasingly diverse range of business models, offering investors a growing choice of entry and exit routes.

“The UK is really good at inventions in biotech – like monoclonal antibodies, for instance, a UK technology that transformed the bio-therapeutics field. This is a sector where inventions and discoveries are enormously valuable. Markets are global, and often unfulfilled. New products grow new markets, including for example in many rare diseases, where the availability of treatments is helping more patients be diagnosed and treated.”

“Biotech is developing new product modalities, like cell and gene therapies, which create waves of interest and investment. These waves are not short-lived fashions, though: they endure, as understanding builds and as regulatory acceptance grows. Investors do not need to understand the details of the actual technologies to appreciate that they are important, that they have come of age.”

“There is a huge diversity of business models in biotech, and with that, a widening choice for investors. Today's biotech companies do not always simply license their assets to Big Pharma in early or mid-stage trials. That is just one model. Companies can move up the value chain and further develop their own products. In the UK, we have experienced managers that understand this and have lived through the different stages of biotech company maturity. We've seen companies [like gene-therapy player Orchard Therapeutics] rapidly raise money and get a product to market. It doesn't always need to take 15 years and cost \$2 billion.”

Exchange Traded Funds

Exchange Traded Funds (ETFs) pool together a range of stocks (or other assets, like bonds or commodities) within a single, open-ended investment fund. Shares in this entity are then traded on the market like any other share. ETFs provide investors a proportional stake in all the assets held within the ETF basket. Many track market or sector benchmarks, and aim to match the returns of that benchmark or index. ETFs tend to focus on larger, more liquid securities. Because ETFs are quantitatively managed – using data – there is little or no ‘active’ investment decision-making; this means fees are lower than for managed funds.

Investment Trusts

Investment Trusts are, like unit trusts, run by fund managers. Yet the key difference with unit trusts is that they are closed ended: the number of shares in issue does not vary according to investor demand. Instead, fluctuations in demand mean that the price of the shares can trade at a (sometimes significant) premium or discount to the value of the underlying assets. Typically, the shares of an investment trust will be listed on the stock exchange so can be bought and sold relatively easily.

Investment trusts do not suffer from the same liquidity risk as an open ended vehicle, as the fund manager does not need to sell the underlying investments in order to satisfy investor redemptions. As a rule of thumb, investment trusts are better suited for more illiquid, or smaller market cap investments.

Venture Capital Trusts

More commonly known in the UK as VCTs, these are a tax efficient variant of the investment trust. VCTs are intended to channel investment toward smaller companies that meet certain financial criteria. AIM-listed groups, as well as some private companies, qualify for VCT investment. In return for investing in higher risk, often earlier stage investments, investors in VCTs benefit from attractive tax reliefs.

Investment Companies/IP Commercialisation Vehicles

Investment companies and intellectual property (IP) commercialisation vehicles are also structured as closed-ended companies, and are often listed. But unlike Investment Trusts and VCTs, typically managed by a third-party, they tend to have in-house management who contribute their expertise to investee companies. IP commercialisation vehicles scour academia for the best ideas and IP, helping turn them into start-ups. They may work across several academic institutions, technologies and geographies, putting relatively modest sums to work across a range of projects

Listed IP commercialisation vehicles offer investors exposure to the front-end of innovation. They spread risk by investing in multiple ideas from across various source institutions, protecting investors from the downside of holding shares in individual quoted or unquoted companies, which may be highly illiquid.

Yet these groups are still dealing in the very early stages of drug discovery and development, meaning the chances of success remain low for any given project. Further, some IP commercialisation vehicles may not be in a position to invest through later stages of development. This may dilute their holding, potentially limiting up-side if a project does succeed.

Less widely accessible vehicles (venture capital funds)

Venture capital funds invest in un-listed start-ups, or small-to medium companies with strong growth potential. These make up the majority of biotech companies. Managed by experienced sector-specialists, venture capital funds generally offer investors a higher-risk, higher-return profile than funds, as described above, which invest primarily in listed groups.

VC funds are typically not available to retail investors. VC investors – sometimes called “limited partners” – tend to be institutions, endowments, pension funds or other corporate entities. Some companies that run VC funds are themselves listed on the stock exchange, however, offering another route for non-specialists to gain exposure to the sector.

Life sciences and healthcare VC funds may focus on particular therapy areas, company models (such as platform-technology groups) and some may include medical technology, digital health and/or health data analytics-focused companies, as well as biotech and small pharmaceutical companies. Some VCs also manage public funds, and/or invest in public companies, including taking their own private holdings public through an IPO (cross-over investing).

EIS funds

Like VCTs, Enterprise Investment Scheme (EIS) funds offer a tax efficient means of investing in high-risk, private or AIM-listed businesses across many sectors, including biotechnology. They are primarily aimed at individual investors but, unlike VCTs, they are not listed and must be accessed via advisers. They invest in the same way as traditional venture capital funds but can only invest in companies certified EIS eligible by HMRC so that individuals investing in the fund can access the tax relief. The EIS scheme offers investors income tax relief on up to £200,000 per year and tax-free dividends and gains, if they are held for at least three years. Investors can also receive EIS relief when investing directly into eligible businesses.

Glossary

Antibody: proteins produced by our immune system to fight off invading pathogens. Antibodies are a very important class of drug therapies, and are also used as research tools. Many targeted cancer drugs, including immuno-therapies (see below), are antibodies.

Biologic: a protein-based therapy produced from microbes or cell cultures, typically taken as an injection. Also referred to as “large molecule” drugs.

Biopharma: used to refer to therapeutic-focused biotech companies, often but not always the more developed companies of the sector.

BRCA: an abbreviation for “BRCA Cancer gene.” BRCA1 and BRCA2 are two different genes that have been found to impact a person’s chances of developing breast cancer.

Cell therapy: treatment that involves extracting certain cells from a donor or patient, engineering them outside the body and re-injecting them.

CAR-T: a type of cell therapy involving a class of immune system cell called T-cells. These cells are engineered in the laboratory to target a specific protein found on some cancer cells. CAR-T cell therapies are approved for certain forms of blood cancer.

CRISPR: a technique that allows scientists to rapidly, easily and precisely edit DNA. Prior to the discovery of CRISPR tools about a decade ago, genome-editing was cumbersome and expensive. CRISPR stands for ‘Clustered Regularly Interspaced Short Palindromic Repeats’; they are naturally-occurring chunks of repeated DNA, evolved among bacteria to fight off viral infection.

DNA: de-oxyribonucleic acid – a self-replicating material that carries our genes and related genetic information.

Gene: a sequence of nucleotide molecules within our DNA, some of which carry the instructions for making proteins. A gene may also be thought of as a unit of heredity, transferred from parent to offspring.

Gene therapy: treatment that involves replacing a faulty or missing gene with a working copy.

Immuno-therapy: treatments that harness the body’s immune system to help fight disease. ‘Immuno-oncology’ refers to immunotherapies used in cancer.

Indication: the condition and other characteristics of a patient for whom a medicine is authorised to be prescribed to.

Orphan drug: a product for a rare, life-threatening or very serious condition affecting fewer than 5 in 10,000 people (in the European Union) or fewer than 7.5 in 10,000 (in the US). Orphan drugs enjoy various R&D, intellectual property and marketing incentives, plus fast-track regulatory pathways.

Personalised or precision medicine: the use of genetic or biological markers to determine whether or not a patient will respond positively to the medicine.

RCT: randomized controlled trial. RCTs have been considered the gold-standard in trial design, aiming to reduce bias and assess an intervention's efficacy and safety as accurately and fairly as possible. Patients are randomly assigned to receive either the experimental drug, or a control (which may be a placebo, or the standard of care). If neither they nor the doctors know which intervention they are receiving the trial is said to be 'double-blinded'. Many trials of drugs for very rare, serious diseases are not RCTs; they may be un-blinded (open-label) trials of very small numbers of patients, and may not include a traditional control arm.

RNA: ribonucleic acid – a type of molecule that carries information from the gene to cells' protein-making machinery. Some biotechs are trying to develop drugs that use messenger RNA to impact the expression of certain disease-critical genes. In 2018, the FDA approved the first treatment that silences gene-expression by interfering with RNA. Alnylam's Onpattro (patisiran) is a "small-interfering RNA" (siRNA) molecule, approved for a very rare condition that causes nerve disease and affects the heart.

Small molecule: chemical medicines below a certain size threshold that can be synthesized in the laboratory and are usually taken in pill form.

Virus: a small biological agent that requires a living host for replication. Viruses are often infectious, but can be engineered to act as carriers or vectors to transport therapies into cells.

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About the BIA

Established over 25 years ago at the infancy of biotechnology, the BioIndustry Association (BIA) is the trade association for innovative life sciences in the UK. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

Our members include:

- Start-ups, biotechnology and innovative life science companies
- Pharmaceutical and technological companies
- Universities, research centres, tech transfer offices, incubators and accelerators
- A wide range of life science service providers: investors, lawyers, IP consultants and IR agencies

We promote an ecosystem that enables innovative life science companies to start and grow successfully and sustainably, and we do this through *Influence, Connect, and Save*.

Influence

The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators, to patient groups and the media. We also work with organisations at an international level to ensure that UK biotech is represented on the global stage including Europabio, EFPIA and ICBA. BIA is the key thought leader for the sector – working across a wide range of related issues including policy, finance, science, regulatory, legal and talent.

Connect

The BIA provides many varied opportunities for life science leaders to connect with each other – to network, share and learn from experience, to access sector thought leadership and to take key issues forward. From the famed BIA Gala Dinner, to the CEO & Investor Forum, Women in Biotech networking evenings, quarterly committee meetings and our many regional events, to name but a few, the BIA provides access to a highly respected and diverse network. BIA also works to ensure that we provide opportunities and promotion for our members internationally – through panels and networking events at major events overseas, we are raising the profile of the UK as a global hub. We know that promoting what you do as an organisation is important, and we help organisations to raise their profile – at events and through our online presence and communications.

Save

For many of our emerging members (and a good number of well-established ones too) the BIA Business Solutions Scheme provides significant savings that are helping them to grow more cost-effectively. We believe this is the most competitive scheme of its kind in the UK.



For more information about the BIA and our finance work, please contact info@bioindustry.org.



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Online and in person with industry leaders

40+ events across the UK
760+ organisations
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5,000+ readership

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