FUTURE OF PHARMACEUTICALS

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RESEARCH AND DEVELOPMENT

Generic re-engineering: how an R&D hub can aid the NHS

With a mission to develop advanced drug production techniques, a newly built innovation centre in Glasgow offers solutions to several problems facing the service and the UK pharma industry

John Illman

A pioneering new R&D facility, to be officially opened shortly, is set to streamline pharmaceutical production in the UK. Experts in the field believe that the work of the £56m Medicines Manufacturing Innovation Centre (MMIC) has the potential to save the economy hundreds of millions of pounds a year.

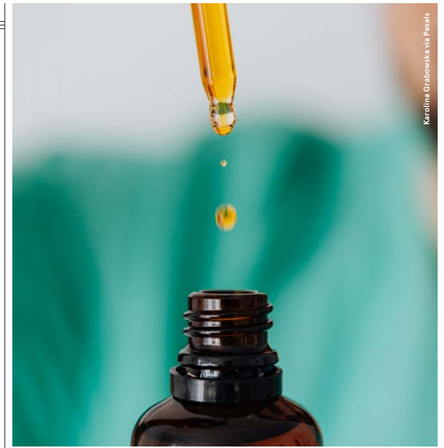
The centre, located by Glasgow Airport, is the outcome of a public-private collaboration involving founding industry partners GSK and AstraZeneca, Scottish Enterprise, UK Research and Innovation, the Centre for Process Innovation and the University of Strathclyde.

Professor Clive Badman, executive director at the university and former head of pre-competitive collaboration at GSK, has played a leading role in the centre's creation. He explains that one of the main reasons for its existence is to find a more efficient alternative to what's been the industry's standard procedure for the past 100 years: multi-step batch manufacturing. The stop-start nature of this approach means that the entire production process can take as long as two years. If producers were to adopt so-called continuous manufacturing on a large scale instead, it should enable them to cut the time down to six months at most.

Batch manufacturing is notoriously inefficient. In a research report last year, PwC noted that, 15 years ago, "it was estimated that $50bn was lost as waste each year in the US alone due to inefficiencies of batch production. Since then, very little has changed."

Continuous manufacturing has been shown to reduce capital costs by up to half, downstream waste by 60% and greenhouse gas emissions by as much as 80%.

Crucially, continuous manufacturing could make the UK more self-reliant and help to restore the fortunes of its pharma sector. According to the Association of the British Pharmaceutical Industry, the sector's exports fell so drastically in 2010-20 that its trade balance sank from an £8.9bn surplus to a £920m deficit over that period. More than 75% of generic (off-patent) drugs prescribed on the NHS are estimated to contain at least one component made in India or China, while many others are wholly manufactured abroad. Generics account for 90% of British prescriptions.



Karolina Grabowska via Pexels

Although these imports from China and India are tested by the UK Medicines and Healthcare Products Regulatory Agency, many in the industry are still concerned about their quality. They are also worried about the prospect of China weaponising drugs, just as Russia has been weaponising energy.

But the problems don't stop there, as Badman explains. "Disruptions from Brexit and the pandemic have meant that, despite having held contingency stocks, we have been running short of critical drugs. This has led to the prescription of second- or even third-line choices."

The NHS has reported that 1,700 medicinal products have been in short supply since the start of the pandemic. Last October, for example, the NHS Cambridgeshire and Peterborough Clinical Commissioning Group alerted local healthcare professionals to shortages of more than 30 drugs, including vital ones such as the painkiller diamorphine and the antidepressant fluoxetine.

This supply crisis has been widely attributed to the market's haphazard, free-for-all nature. Costs are set by the so-called drug tariff price – the amount the NHS pays pharmacies for prescription generics.

"Pharmacists are encouraged to buy generic drugs at a cost below the tariff price to give them a profit," says Professor Mike Hannay, a member of the Royal Pharmaceutical Society's governing assembly. "This is great for the NHS – it keeps driving down prices."

More than a billion generic prescriptions are written each year, saving the NHS more than £13bn annually, according to the British Generic Manufacturers Association. Newer branded products are far more expensive. It's not unusual for the cost of developing one drug to run into billions, but in the high stakes of pharmaceutical roulette, nearly 90% of medicines in development – so-called candidate drugs – never reach the market.

The cost savings that the NHS achieves with generics enable it to prescribe innovative new drugs. Last year, for instance, five-month-old Arthur Morgan became the first NHS patient to receive a one-off gene therapy medication for spinal muscular atrophy (SMA). Untreated SMA is the leading genetic cause of childhood death. The drug in question, Zolgensma, has a 'list price' of nearly £1.8m per dose. The NHS has not disclosed how much it paid for his treatment.

There is a conundrum dominating the debate about how to pay for NHS drugs: price-cutting by the suppliers of generics has been pushing manufacturers out of the UK.

"This is what happens in a commodity market – it's supply and demand," Hannay says. "Prices get so low that one manufacturer after another leaves the market until there is only one left. At that point, the prices of generics go through the roof."

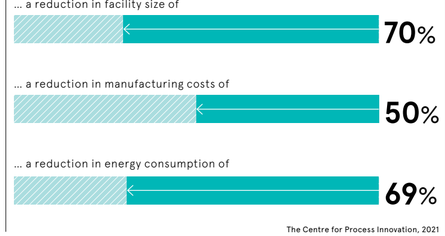
In 2020, *The Pharmaceutical Journal* reported that the NHS's medications bill had increased by an estimated £76m in only two years because of drug tariff price hyperinflation. For instance, the drug tariff price of risperidone, a widely used generic antipsychotic, had leapt by 1,736% since 2018.

Extreme price volatility has become a feature of this market, notes Hannay, who adds: "We buy medicines at a 'spot price' on the day. No other industry would do this."

But Badman is confident that the MMIC can address the problem through its work to transform how drugs are made in the UK. The efficiency improvements promised by the development of continuous manufacturing techniques "should enable British companies to produce generic medicines at a comparable cost to that incurred by Indian and Chinese exporters", he says.

If the MMIC succeeds, it should improve the NHS's security of supply, help the domestic pharma industry and boost both the local and national economy – a shot in the arm with no adverse side effects.

CONTINUOUS MANUFACTURING COULD RESULT IN...

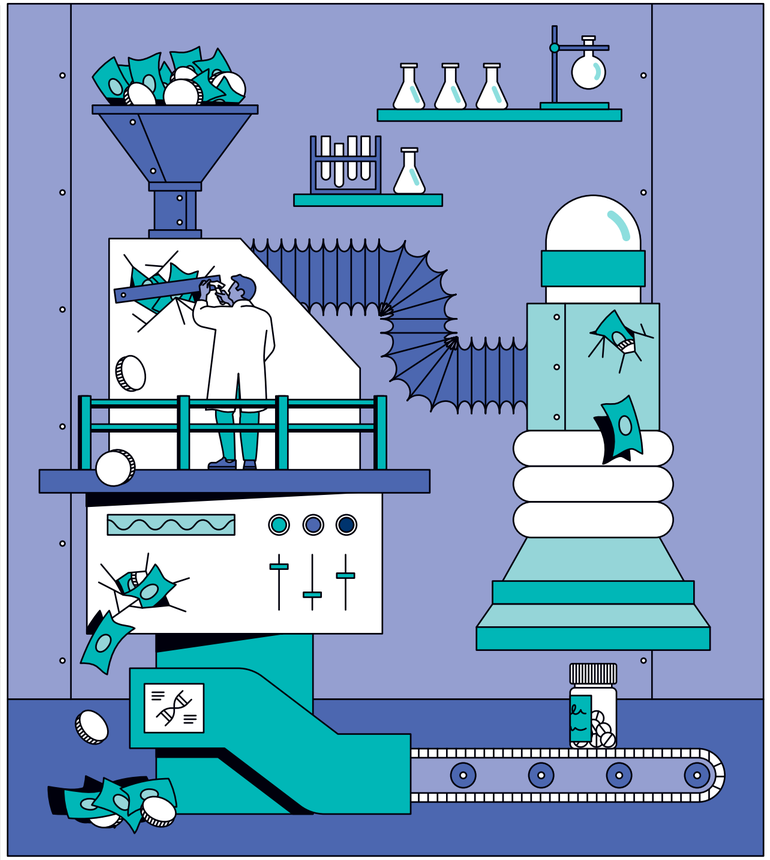


The Centre for Process Innovation, 2021

DRUG DISCOVERY

Eroom for improvement

For big pharma in particular, the drug discovery process is a notoriously protracted and profligate exercise. Does it really have to be this way?



Nick Easen

Despite incredible advances in science, we still find it hard to bring new pharmaceutical products to market cost-effectively. It's why Eroom's law was coined 10 years ago. This states that the real cost of developing a new drug roughly doubles every nine years. It's so named because it's the reverse of Moore's law – an observation that the semiconductor industry has managed to double the number of transistors it can cram on to a microchip about every two years.

There has been a slight improvement in pharma productivity since 2010, but this pales in comparison with the preceding slump. And there is a chance that Eroom's law could again exhaust resources and push costs back up. It retains a seemingly inexorable gravitational pull on the sector's efforts to improve its R&D efficiency.

Professor Chris Molloy is CEO of the Medicines Discovery Catapult, a government-backed not-for-profit innovation centre. He points out that "competition between firms targeting the same 'new' biology has led to 4,400 ongoing clinical trials assessing certain antibodies for cancer cells. There is neither the breadth of biology nor the market capacity to support the outputs of these trials. Eroom's law was kept true by a cohort of increasingly large and complex companies competing over similar approaches to similar biological problems. There have also been decades-long inefficiencies in clinical trials, which still account for more than 60% of total R&D costs."

Defying Eroom's law requires a "multifaceted approach, not just a focus on R&D costs", says James Barlow, professor of technology and innovation management at Imperial College Business School. "We need to look at the overall drug delivery pipeline and the processes supporting this."

The growing number of cheap generic medicines coming to market not only raises the bar for new pricier drugs; it also deters investment in therapy areas where generics exist. Why spend heavily on developing an expensive 'super-drug' when lower-cost alternatives are already available and doing an adequate job? Yet, if drug discovery were a more productive process, gains could be achieved.

The failings of drug discovery are complex. They do not depend on one sector, group of companies or processes. Inefficiencies occur all the way along the value chain. Empowered by new data, AI technologies such as machine learning could help here (see panel, opposite page), but the availability – or lack thereof – of the biological data these systems require to work properly is a limiting factor.

Professor Jack Scannell is an industry consultant who led the team of academics that proposed Eroom's law in a paper published by *Nature* in 2012. He argues that "the biggest challenge is that we often make the wrong decisions *before* clinical development starts. We need to devote much more intellectual effort to evaluating disease models before we invest in drugs. There is a lot of mileage in techniques that tell us more about disease in people, with insights that can be translated back into tools that are used in R&D."

Scannell continues: "We are short of good decision-making tools, whether it's animal and in-vitro models or human experimental medicine methods that tell us if candidate drugs will be useful or not. The financial incentives are also wrong. They push investment towards novel chemistry, which generally isn't the bottleneck."

The fact is that novel chemistry is the most investable form of pharmaceutical innovation, because it can be protected more easily by strong patents.

The key to finding better drugs in the lab will require a deeper understanding of disease biology and more effective methods of modelling the effects of diseases. This could be aided by better R&D collaboration that encompasses big pharma, biotech companies, academics, regulators, policy-makers and patient groups.

Dr Jennifer Harris, director of research at the Association of the British Pharmaceutical Industry, is a firm believer in the benefits of pooling resources and cooperating more closely on research.

"This is fundamental to the discovery and early development of new medicines," she says. "It's vital to create a dynamic ecosystem that inspires innovation through collaboration across disciplines, sectors and borders."

Big pharma can also learn from observing practices in fields with a demonstrably strong focus on efficiency – the hi-tech sector, for instance. Recruiting people from such industries could help as well.

"There is too much inefficiency in the costs of drug development and there is not enough focus on lean teams, virtual companies and outsourcing," says Chris Garabedian, CEO of Xontogeny, a biotech accelerator. "When a pre-clinical stage biotech company has 50-plus employees, as well as 10 senior executives, inefficiency is likely. At least 80% of a programme's budget should be going towards advancing R&D and no more than 20% to non-research activities. This is not always the case."

Molloy notes that some successful smaller players in drug discovery have defied Eroom's law recently. "Their costs of capital and appetites for risk contrast with those of big pharma, which is running only 20% of the world's clinical trials. Risk-takers such as Moderna and BioNTech, which cracked the Covid pandemic, should be fresh in our memories," he says.

Real-world research also offers considerable potential. This involves collecting data arising from the routine delivery of healthcare services, rather than controlled experiments. Interest in this information has proliferated in recent years. It has the potential to both enrich and expedite the R&D process.

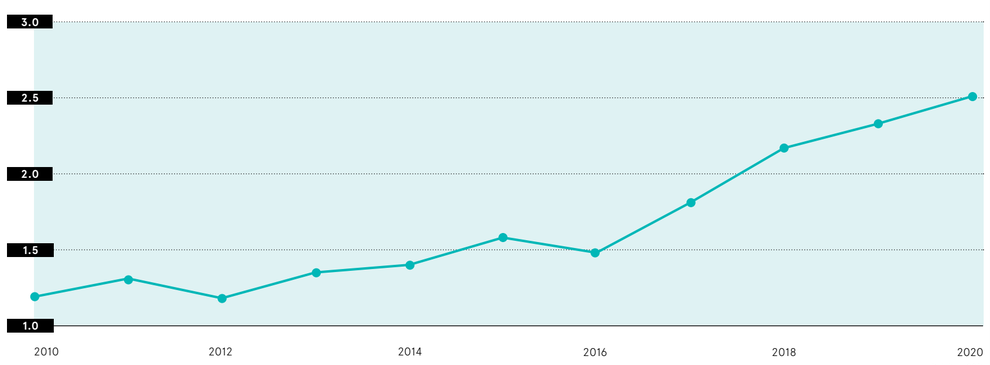
This approach was used effectively during the early stages of the Covid crisis. The rapid roll-out of vaccines and other treatments would have been impossible without the aid of real-world data.

Harris notes that "the ability to collate such data, analyse it and learn from it is central to our ability to develop new medicines and improve patient outcomes. Bringing health data together from different sources will be key to better understanding human biology and drug responses."

For all the productivity problems the drug discovery sector faces, it's more able than it ever has been to determine what its real bottlenecks are. The next few years will see whether it can overcome these.

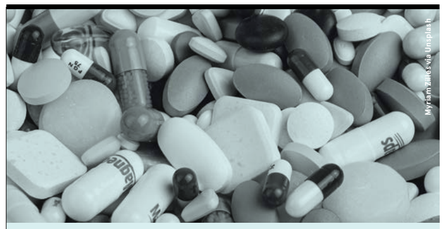
THE STEADY RISE OF DRUG DEVELOPMENT COSTS

Average R&D cost among 12 global biopharma companies to develop a pharmaceutical compound from discovery to launch ($bn)



Deloitte, 2021

> **It's vital to create a dynamic ecosystem that inspires innovation through collaboration across disciplines, sectors and borders**



Myron Rolle/Unsplash

How AI can aid drug discovery

Like many other industries, pharma has great hopes for artificial intelligence. Indeed, the first drugs designed mainly by AI systems are already being investigated in clinical trials.

In genomics, where vast swathes of genetic data are becoming available, machine learning is starting to play a significant role in choosing drug targets. Funding for AI technology, particularly in drug discovery, has also boomed in recent years. Machine-learning systems, for instance, are helping to map disease pathways, mine literature and analyse data.

But all the hype surrounding AI's potential can be distracting, according to Jack Scannell. He argues that it "shouldn't blind us to the fact that disciplines that have fallen under the AI rubric have been useful for decades. Computational chemistry, chemo-informatics, structural biology, computational genetics – long part of the mainstream in the drug and biotech industries – are being branded as 'AI'."

The biggest factor limiting the effectiveness of AI in pharma is the amount of biological data that's available to crunch. Generating better data will help to train the algorithms, but this is costly and takes time.

"A lack of high-quality healthcare and biomedical research data that's accessible and mineable is limiting the potential of AI," says Dr Martin-Immanuel Bittner, CEO of drug discovery firm Actoris. "Any drug discovery programme is a series of decisions. We can make better ones with better data. If I could change one thing about current practice, I would want it to be based on the best possible data, generated reproducibly at scale in a physiologically meaningful way."

There are some areas in which AI is aiding significant advances. They include drug chemistry, protein structures and predictive modelling, yet these aren't typically the rate-limiting steps in the R&D process.

"AI systems are well suited to recognising patterns in data. They have unprecedented capacity and scalability," says Chris Molloy. "The skill is to feed them with interconnected, multifaceted data. British companies such as Exscientia, BenevolentAI, PhoreMost and Healx have trained their systems to analyse decades of structured chemistry, biology and literature data to help them obtain otherwise improbable insights, which will guide their R&D decisions."

AI can certainly be an extremely powerful R&D tool, but it's clear that the industry is still learning the extent of these powers and where best to apply them.

> **When a pre-clinical stage biotech company has 50-plus employees, as well as 10 senior executives, inefficiency is likely**

INSIGHT

'The scale of the challenge means we need to collaborate'

Pinder Sahota, president of the Association of the British Pharmaceutical Industry and general manager at Novo Nordisk UK, on the sector's quest for sustainability

Q What are the components of sustainability in the pharmaceutical industry?

A In a broad sense, we're looking at the environmental impact of the research, manufacturing, distribution and disposal of medicines.

The industry is committed to minimising its impact on the planet. We have been involved in environmental initiatives since the early 1990s. Companies are investing in the R&D of greener products, as well as more sustainable manufacturing and distribution practices. The goal is to deliver medical innovation to patients in ways that protect the environment as well.

Companies are also working on initiatives to cut carbon emissions across their own operations, as well as those of their suppliers. But sustainability isn't only about minimising greenhouse gas emissions. Initiatives to recycle, reduce waste, save water and minimise the impact on the environment from the normal use of the medicine are all vital.

All companies that are members of the International Federation of Pharmaceutical Manufacturers & Associations have sustainability commitments. Many have set theirs using the Science Based Targets initiative or other widely recognised standards. Some are further ahead than others, but every firm takes environmental action seriously.

Q How can the sector best address such challenges?

A The industry needs to look at its wider footprint. It's not only about knowing the direct impact we have on the environment; it's also about understanding the effects our suppliers have as they work for us and the effects our patients have as they use our medicines. We must reimagine our entire value chain. Without the ambition, commitment and investment to do that, we'll never have an accurate picture of the footprint we're reducing.

The scale of the challenge means we need to collaborate with others. A good example is the Energize initiative, where 12 pharmaceutical companies are working with energy suppliers to accelerate the adoption of renewable electricity and reduce greenhouse gas emissions in the pharmaceutical value chain.

We fully support the NHS pledge to reach net zero with its suppliers by 2045. Pharmaceuticals have been estimated to account for between 12.5% and 25% of its carbon emissions in England, with 5% attributed to certain asthma inhalers and anaesthetic gases. Several firms are already making lower-carbon inhalers and are investing heavily in researching and trialling alternative types of gas for inhalers that make them much better for the environment. That's the type of innovation that needs to be encouraged.

Q What role should industry regulators be playing here?

A It's important that companies can work with the authorities globally to solve the environmental challenges we face. We've seen during the pandemic that the industry can bring real benefits to the table, working with the government, the NHS, academia and other parties. Addressing the global climate crisis will take a similar kind of collaboration, maybe on an even greater scale. Forums like the upcoming COP27 meeting will play a key role in enabling such work.

One area where further collaboration would help is regulation. The pharmaceutical industry is highly regulated in areas ranging from patient safety to environmental sustainability. If a company makes changes to a medicine or its packaging for environmental reasons, we need to see various regulators coordinate their policies so that we can generate the data they require to demonstrate that the product continues to meet the highest standards.

Only by working with regulators, governments and global health systems can we go further and faster in meeting our environmental goals.

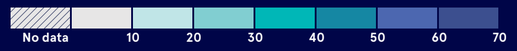
Pinder Sahota
President,
The Association of the British Pharmaceutical Industry

GENERIC DRUGS

Although most revenue in the pharmaceutical industry is generated by major branded medicines and products, sales of generic drugs have continued to grow. Indeed, in some European countries, generics account for a significant share of the prescription drugs market. While there are many reasons to be thankful for the innovation in big pharma, generics have been proving invaluable in terms of both affordability and availability

MARKET SHARE

Market share of generics in selected European countries in 2020



European Federation of Pharmaceutical Industries and Associations, 2022

$338.4bn

Total cost saving achieved in the US healthcare system by using generics and biosimilars in 2020

Association for Accessible Medicines, 2021

37% of global medicine spending is expected to be on drugs other than original brands by 2026

IQVIA, 2021

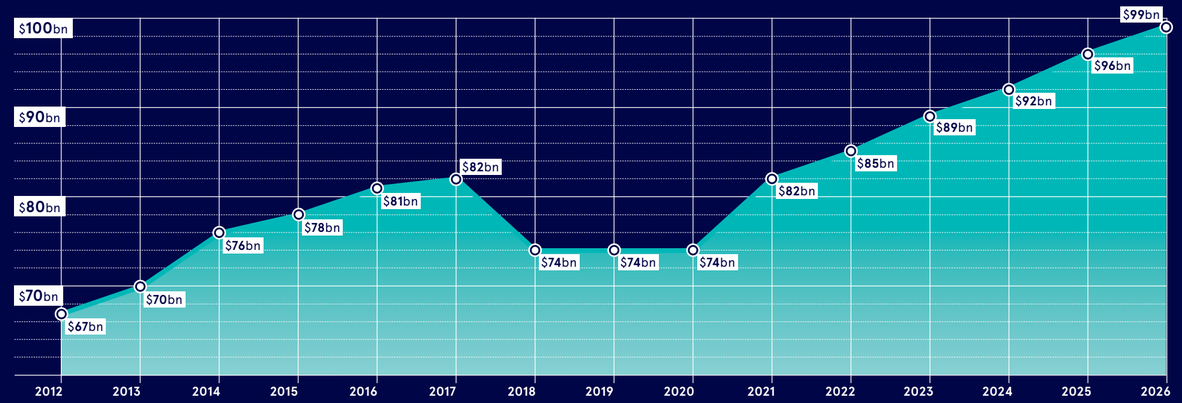
$497bn

Projected value of the global market for generic drugs by 2025

KPMG, 2020

GENERIC REVENUES

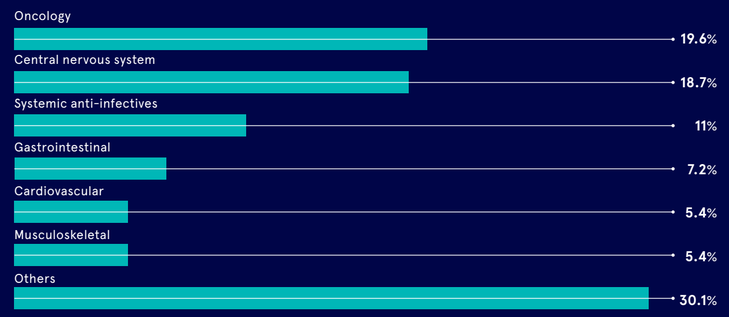
Actual and forecast global sales of generic prescription drugs in 2012–26



Evaluate, 2020

OPPORTUNITIES FOR GENERICS

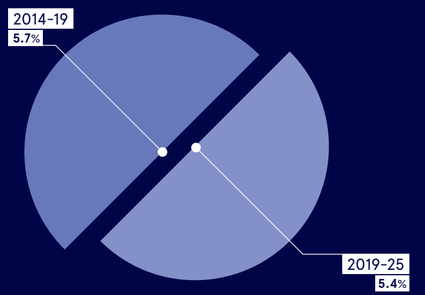
Potential for manufacturers to produce generics, based on percentage of patent expirations by therapeutic area in 2020–26



KPMG, 2020

MARKET GROWTH

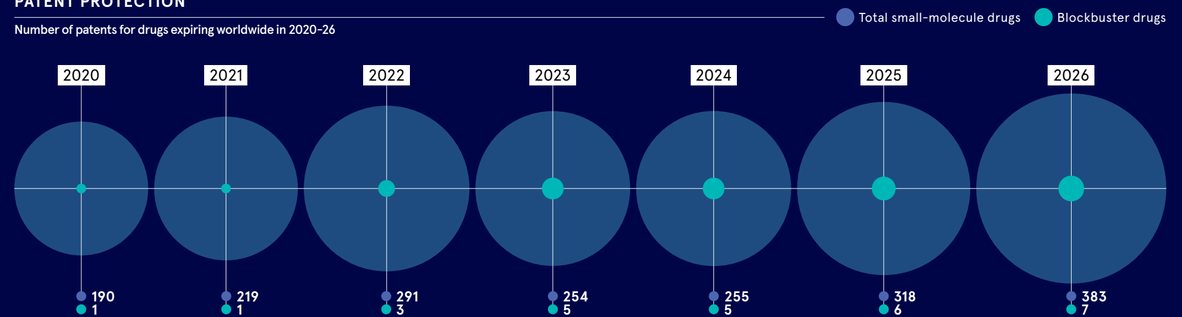
Actual and forecast compound annual growth rate of the generics market



KPMG, 2020

PATENT PROTECTION

Number of patents for drugs expiring worldwide in 2020–26



KPMG, 2020

Extending the role of big pharma in search of easier treatment

Pharmaceutical companies such as Accord Healthcare have become far more than medicine manufacturers, in recognition that the effectiveness of a medicine may be determined by how it is delivered – as an injection or pill, for example. Patient advisory groups are advising on what are known as `drug delivery systems'

History has shown repeatedly that crises, such as pandemics and war, accelerate the pace of scientific progress. So it has been with Covid-19. It can take 10 years or more to develop a vaccine. It took less than a year to develop successful Covid-19 vaccines thanks to unprecedented international cooperation.

But innovations have not been restricted to new developments to restrict or treat Covid-19. The pandemic has acted as a catalyst for exciting developments in remote and digital care for patients who struggled or were anxious about attending clinic appointments during lockdowns.

> **We know that there is more work to do, but again, it is worth stressing: we realised during the pandemic that our support doesn't have to just stop at chemotherapy medicines**

This has extended the role of companies like Accord Healthcare, one of Europe's fastest growing pharmaceutical companies. Accounting for a third of all injectable chemotherapy for cancer in Europe, it is researching innovative drug delivery systems to maximise the efficiency of chemotherapy and supporting to minimise symptons.

This is a huge challenge because chemotherapy has extensive side effects, which can include extreme fatigue, nausea, hair loss and increased vulnerability to infection. The many types of drug delivery systems include capsules, tablets, injections and infusions (injections administered over a long period, sometimes hours).

Enabling patients to self-administer drugs at home became critically important during the pandemic. Self-administration can be more convenient, potentially reducing pressure on over-stretched hospital and GP practices.

This is why Accord is collaborating with healthcare professionals and patient groups to try and make self-administration as easy as possible. Many cancer treatments require injections or infusions.

The company, which has 500 research scientists, is looking for ways to reduce infusion time, make injections easier to give and receive and reformulate injections into tablets. This could not only help patients, but may also save the NHS time and resources – reducing the need in some cases for hospital or GP visits. There are already some injections patients can administer themselves.

Accord's collaboration with healthcare professionals and patient groups has led to investments in a range of innovative options to help patients who find self-administration of injections very difficult; for example, those with poor dexterity or needle phobia and so on. This was a big problem during the pandemic for patients who were immunocompromised or frail and were unable to visit hospitals or GPs.

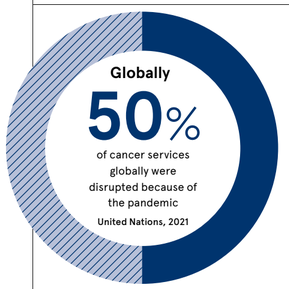
Infusions, administered in clinics, can be especially challenging for patients. Joseph Dunford, vice-president, speciality brands at Accord, says: "I know how hard it is for patients. Some patients may struggle sitting in infusion chairs for hours. I don't think that we will eliminate the need for infusion, but we can try and make some incremental gains. For example, one less trip to hospital for a patient could be considered progress."

Collaborating with patient groups is key. Dunford notes: "These groups do astonishing work in raising awareness about cancer, alerting people to possible threatening symptoms and encouraging them to flag up any concerns they have to their doctors.

"They are also there for patients who have just had a cancer diagnosis. People may need both psychological and practical support, and someone to lean on during what may be a very frightening, lonely time."

Newly diagnosed cancer patients can experience sadness, anxiety, anger and sometimes a sense of helplessness. And, of course, it is not only the individual patient who is affected. Family members may also go through turbulent, emotional ups and downs.

THE IMPACT OF COVID ON CANCER CARE



UK

50,000

The estimated number of missing cancer diagnoses in the UK

Macmillan Cancer Support, 2020

Europe

1 million

cancer patients across Europe could have been undiagnosed

European Cancer Organisation, 2022

Research priorities

Prostate cancer is among Accord's current focuses, particularly because it is the most common cancer among men in the UK. Moreover, more men are developing the disease as the population gets older. Prostate cancer is another example where Accord sees its role as being far more than just a medicine manufacturer.

While recent campaigns have increased awareness of the signs and symptoms of prostate cancer and encouraged more open debate, prostate cancer still remains a sensitive and often stigmatised topic. This, in turn, can discourage men from going to the doctor.

The invasive nature of tests for prostate cancer, and fears over the impact of surgery, radiotherapy and hormonal treatment, including disruption of sexual performance and libido, can be very concerning for patients. Reduced energy levels, insomnia and challenges with urinary and bowel function can also impact productivity and patients' ability to engage in social activities.

> **I know how hard it is for patients. One less trip to hospital could be considered progress**

1 in 7

men in Europe will develop prostate cancer before the age of 85

European Association of Urology, 2020

All of these things underline a great challenge for the pharmaceutical industry, academic researchers and patients and their families.

Pharmaceutical innovation

Accord's pipeline encompasses treatments for prevalent tumour types, including breast cancer, in addition to haematological and cancer supportive care therapies. The company has 20 treatments scheduled for launch over the next five years.

It is also at the forefront of the development of so-called biosimilars. These medicines are clinically equivalent to biological medicines derived from living cells. There has been increasing interest in biosimilars over the last few years as biologic 'originator' medicines have come off patent. Biological medicines have provided transformative treatments for inflammatory and autoimmune diseases and hormone deficiencies.

The use of cost-saving biosimilars has saved the NHS hundreds of millions of pounds, while giving ever increasing numbers of patients access to state-of-the-art medicines. Providing value for money is an integral part of the Accord philosophy and perhaps explains why the company has become one of Europe's fastest growing pharmaceutical companies.

For more information please visit accord-healthcare.com

accord

This article has been paid for by Accord Healthcare

Q&A

Our support doesn't have to stop at chemotherapy

Joseph Dunford, vice-president, speciality brands at Accord Healthcare highlights the company's commitment to patients and the critical lessons of Covid-19

Q Can you put into perspective the scale of the cancer challenge?

A The patient is at the centre of everything we do. We are driven by the knowledge that cancer is the second biggest cause of death in Europe – 1.9 million deaths annually, plus 3.7 million new cases, according to the World Health Organization. The pandemic has created an additional major problem. The charity Macmillan Cancer Support, with whom we collaborate, has estimated that there were around 50,000 'missing' diagnoses across the UK – meaning that compared to a similar timeframe in the previous 12 months, there had been 50,000 fewer cancer diagnoses.

Q Patients are generally speaking far better informed these days. How significant is this in terms of their physical and mental health?

A It is well established that empowering patients with knowledge about their condition may help to support them through the initial stage of their illness. But it has to be reliable knowledge. Where do we all turn for knowledge? Often we start with a Google search. Unfortunately, the quality of information on the internet is very variable. This became horribly clear during the pandemic, when appointments were postponed and patients were afraid to attend hospital out-patient appointments.

Patients need reliable information at all times – you cannot get an appointment with an oncologist (cancer specialist) at 3am when you are having a sleepless night arising from worry and fear.

That is why in September 2021, Accord contributed to the launch of an oncology patient support app – Unify Health. It was developed with experts from the Royal Marsden NHS Foundation Trust, Care Across (a digital startup focusing on cancer), and Macmillan Cancer Support and the wider cancer community. It offers support and advice to patients to aid their physical and mental wellbeing while undergoing cancer treatment.

Macmillan Cancer Support is one of Britain's largest charities. It provides information about symptoms, care, wellbeing and other support to people affected by cancer; looks at the emotional and practical impact of cancer; campaigns for better care; and runs an online cancer forum for 90,000 people.

What we were looking to achieve with the app was a holistic support system for patients from the time of diagnosis. We wanted to enable them to download relevant information that also linked them to their local pharmacist, another critical source of support.

We know there is more work to do, but again, it is worth stressing that we realised during the pandemic that our support doesn't have to stop at chemotherapy medicines. We can support patients through their journey using tools that are accessible 24/7 and that are tailored to their needs and preferences.

Q Can you say more about pharmacists? There is a view that their skills and expertise are often under-appreciated.

A Absolutely. A report published by the independent think-tank The King's Fund in March concluded that pharmacists working in primary care networks in England were 'under-appreciated' by GPs and often given tasks 'below their competency level'.

Again, working in collaboration with the Royal Marsden NHS Foundation Trust, we have developed a separate app for pharmacists. Oncodemia provides a practical, bite-size training curriculum for community pharmacists who wish to help champion cancer care in the community. It provides advice on how to talk to and assist cancer patients, particularly around managing symptoms and worries.

We felt that pharmacists, just like patients, needed supporting during the recent lockdowns. They were one of a number of vital industries, including supermarkets, who just had to keep going. They were already under-resourced and overstretched and even more in demand as healthcare needs soared.

Accord Healthcare

- Provides a **fifth** of the UK's generic prescriptions (medicines out of patent)
- Accounts for a **third** of all injectable cancer chemotherapy in Europe
- Distributes nearly **1,000** medicines in the UK
- Supplies approximately **20 million** packets of medicine a month in the UK
- Manufactures and distributes medicines in **85** countries
- Has **2,000** employees, including 500 research scientists

Launched only 14 years ago, Accord is a privately-owned company which is developing a major research and development centre in Harrow, north London, due to open in 2023. Cancer will be one of its major focus areas.

The company's portfolio spans oncology, cardiology, neurology, psychiatry, diabetes, pain management and gastroenterology.

BESPOKE DRUGS

Some day, your prints will come

Since the first 3D-printed medicine was approved in 2015, no other drug made using this method has entered the market. But the situation could soon be about to change in a big way

Emma Perry

I magine a future in which one of the crunchy little loops in your bowl of breakfast cereal is your medication, produced by the local pharmacy using a 3D printer and tailored to your taste, your dosage needs and even your genetic make-up.

UK-based research indicates that 90% of drugs work on only 30% to 50% of the population and that adverse reactions account for 7% of hospital admissions. Personalised medicines could increase the efficiency of treatments and reduce the incidence of serious side effects.

Their potential is clear to Deepak Kalaskar, professor of bioengineering at University College London and honorary researcher at the Royal National Orthopaedic Hospital NHS Trust. "If we can reduce the side effects of a dosage, this will improve the patient experience significantly," he says.

Manufacturing such bespoke drugs tends to require numerous ingredients and production processes, which is where 3D printing comes into its own. With the ability to handle a range of materials, it enables layer-by-layer fabrication and can produce small batches relatively economically on demand.

The technology should give healthcare professionals and patients a wider range of treatments to choose from. It could improve drug performance and the patient experience in other ways too. For example, it may be possible to add "further functionalities to final dosage forms", according to Dr Thomas Kipping, head of drug carriers at Merck Group.

He adds: "By embedding a drug substance in an amphiphilic polymer, you can obtain solubility enhancement and super-saturation effects, which can improve your body's uptake of that drug. This can drastically lower the doses needed and so avert unwanted side effects."

The printing process also enables a single tablet to deliver regulated doses of a drug over time, as inert layers can be alternated with those containing the active ingredients.

A report published by BlueWeave Consulting in September has highlighted a rapid expansion in the amount of R&D activity focused on 3D-printed drugs. The firm expects this market to grow from $347m (£326m) in 2021 to $966m in 2028.

Drug development is another field that could benefit from advancements in 3D printing, especially when it comes to cost control. As Kipping points out: "Some drug substances might be a few thousand euros per milligram."

The technology enables both smaller and more complex formulations, he says, "and you may even cut formulation times by half if systems can be optimised".

The facility to print on demand could even help to make pharmaceutical supply chains more sustainable. Traditional production methods can produce a lot of waste, notes Adedamola Olayanju, principal scientist at Manchester Biogel. "What 3D printing can do is reduce this by avoiding excess production. By printing on demand instead of producing to forecast, we may no longer have unused drugs being left to expire," he says.

The biggest challenge is to ensure the quality and safety of printed medicines. For example, printing systems would need to be cleaned thoroughly between production runs to ensure that there is no cross-contamination. The pharmaceutical sector could learn from industries such as car manufacturing, where feedback loops using advanced imaging systems are being applied to provide a layer-by-layer analysis during print runs.

"We could adopt many of these systems to provide safety," Kipping says. "But discussions will be needed with regulatory bodies and machine designers to come up with good solutions."

Pharma's adoption of 3D printing will necessitate new guidance and, potentially, rules from industry regulators on standards of quality and safety. In the US, the Food and Drug Administration (FDA) has completed its analysis of the regulatory challenges created by point-of-care manufacturing.

> **By printing on demand instead of producing to forecast, we may no longer have unused drugs being left to expire**

Dr Thomas O'Connor, deputy director of the FDA's office of testing and research, says: "We hope to be able to share our thoughts in a paper later this year to solicit feedback from multiple stakeholders."

The UK Medicines and Healthcare Products Regulatory Authority has already completed a consultation exercise on such matters. It is looking to "extend the current regulatory framework to enable the manufacture of medicinal products at point of care, including with newer manufacturing methods such as 3D printing".

Only one 3D-printed medicine has been approved and commercialised to date: epilepsy treatment Spiritam (levetiracetam). Nonetheless, this pioneering product has "demonstrated that the pathway is there for 3D-printed drugs", according to O'Connor.

Kipping believes that focusing initially on more straightforward treatments would be a good way to ensure safety and quality.

"I imagine that we could roll out simpler formulations in the short to medium term, with automated feedback loops that don't require such dedicated controlling," he says, but adds that, in the longer term, "patient safety has to be really assured" before the sector goes much further down this path.

As the technology matures, it may even be possible to print medicines personalised to each consumer's genome. To ensure that these work, researchers are bioprinting human tissue on which to test them. The way it reacts to a drug in the laboratory should indicate how it will react in the body.

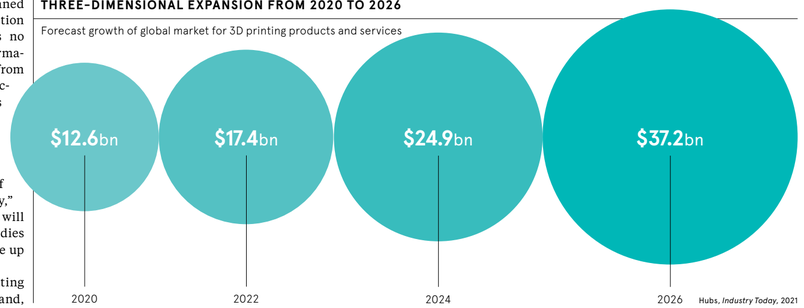
"This is a huge step forward, particularly in areas such as osteoporosis, where our best understanding of the condition used to be based on the results of tests on mice," Kalaskar says.

If the 3D printing of drugs is to be rolled out on a large scale, there are several practical considerations left to address. Not all printers can handle the same materials and manufacture products in the same volumes, for instance, while it would be unviable for a hospital to be operating hundreds of different printers.

The technology is clearly still far from mature, yet it is "moving from concept to industrial stage", Kipping says. "And it is exciting to be part of this evolution."

THREE-DIMENSIONAL EXPANSION FROM 2020 TO 2026

Forecast growth of global market for 3D printing products and services



Hubs, *Industry Today*, 2021

Commercial feature

Supplement absorption levels boosted by unique technology

A technique pioneered to help target cancer therapy has been developed to maximise the positive impact of minerals, vitamins and plant extracts on health

The nutritional-supplements market is one of the fastest growing sectors in the world economy with the public searching for ways to boost their immune system and optimise lifestyles.

The huge interest in good health, generated by the Covid pandemic, has remained. The supplement market, currently valued at $358.8bn, is expected to grow by an annual rate of 6.3% every year to 2030.[1]

The sprint for supplements has been boosted by revolutionary technology that ensures the active ingredients from minerals, vitamins and plant extracts, reach their targets and fulfil their potential.

Traditional ingredients – formulated as pills, powders and gummies – have varying degrees of success with the body's natural defence mechanisms and digestive systems neutralising them to the point that, in some cases, less than 1% reaches the bloodstream.

Liposomal delivery, which was pioneered for targeted cancer treatments, encapsulates the active ingredient in a water-based solution to supercharge its potential to be absorbed by the body – known as bioavailability – and have a positive impact on health.

"Liposomal delivery is a game changer when it comes to distributing all kinds of active ingredients. Our uniqueness is that we have adapted the technology so it can be applied to mass-market products," says Jan Braband, founder and chief executive officer of PlantaCorp, which is a global leader in contract liposomal supplement production.

"Liposomes are incredibly efficient at transporting the ingredient and getting it into the bloodstream so that it can do what it is supposed to. It allows them to get to work. We have levels of 90% bioavailability, which contrasts sharply to other delivery processes that are at 1% and less.

Effective delivery

"The issue with those processes is that the vast majority of the product does not get absorbed and is secreted out by the body, having had minimal effect. Basically, what you pop into your body travels through it and out with waste products with almost no impact."

Studies have shown that iron supplements delivered with PlantaCorp's patent-pending system achieved 398-times greater bioavailability than a non-liposomal method while curcumin was 47-times more effective than comparative products.

The ability of liposomal systems to deliver active ingredients to specific targets in the body has been long established but their manufacture is complex and expensive. Germany-based PlantaCorp's sector R&D expertise enabled it to engineer a cost-effective version for the mass market which is proving a perfect vehicle to deliver the required concentrations of active ingredients across nutritional products.

The company's innovative encapsulation technology works by combining the active ingredient with oil-free phospholipids and water and the solution is then subjected to high-energy ultrasonic waves and high gravitational forces. The process can be adapted to maximise the potential of a range of ingredients and targets within the body.

"It allows the product to work and we have seen clients growing their business alongside ours because of its success," adds Braband, whose company serves operations in 28 countries and has expanded to a new hi-tech manufacturing facility in Hamburg. "It is very rewarding to see customers enjoying success. Bioavailability is a huge challenge but liposomal formulations are the answer."

The liposomal drug delivery market is booming and has a projected market value of $40bn in 2024 and PlantaCorp, which started in 2015 and also operates in the UK, is enjoying huge success with production volume growth estimated at 34.5% for 2021 to 2022 with a 27.8% increase in client base.

Rising demand for supplements

Demand for dietary supplements increased massively during the pandemic and interest in their ability to boost immune systems is still strong. A report showed that supplement use jumped from 29.5% to 71.9% in Asia, from 40.6% to 75.7% in America and went from 30.8% to 68.7% in Europe.[2]

Research conducted by PlantaCorp revealed a trend of strong sales of vitamins and minerals to strengthen immune system with sales of pure vitamin C leaping by 94%, Zinc supplements up by 42% and vitamins A and D sales increased by 35% in the first quarter of 2020. High demand levels have remained as the public continues to seek to improve general health and boost their immune systems.

PlantaCorp has welded its success to a strong ethos of sustainability with its liposomal formulations made from water and GMO-free sunflower phospholipids and sea buckthorn extract is being used instead of chemical preservatives. Glass bottles are the preferred packaging option and its production processes are powered by regionally produced wind energy.

"It is very good to know that our product works and is successful for our clients but I also want to be able to look myself in the mirror and know it is a good product," adds Braband. "We try not to use chemical preservatives and we are constantly updating our processes to enhance our naturalness.

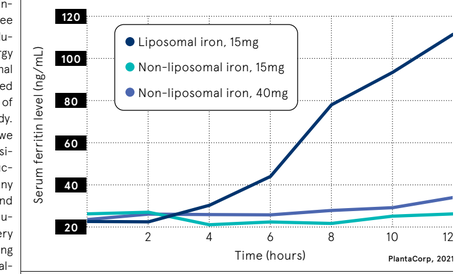
"Liposomal systems have made such a difference to delivering ingredients successfully. The difference between achieving 1% to 10% bioavailability up to 90% is a complete game changer.

"There is so much more that can be achieved and I think we have opened up a door to a new world of possibilities for ingredients and for better health."

1. *Grand View Research, Nutritional supplements market size report, 2022*
2. *Oxford Academic, Current developments in nutrition, 2021*

BIOAVAILABILITY STUDY – IRON SUPPLEMENT

Serum ferritin levels (blood protein containing iron) after single dose of liposomal vs. non-liposomal iron supplements measured over 12 hours



PlantaCorp, 2021

Unlocking the potential of active ingredients

Liposomal technology is making huge advances in boosting the bioavailability from plant extracts which traditionally struggle to get absorbed by the body.

Botanicals, which are preparations made from plants, algae, fungi or lichens, can provide nutritional benefits but they need a carrier to get them into the bloodstream to be effective.

Liposomal delivery allows extracts such as curcumin and quercetin, which have antioxidant, anti-inflammatory and immunoprotective properties, to reach their supplementation potential.

The system's success is significant as the World Health Organisation (WHO) estimates that 80% of countries use medicinal plants as part of their healthcare.[1]

"We are constantly looking at ways to improve our technology so that we can bring more benefit from supplements and plant extracts," adds PlantaCorp founder Jan Braband. "Millions and millions of people around the world want to protect and enhance their health and immune systems and our mission is to help them by refining liposomal delivery technology to get the best from the products they take.

"We are committed to R&D and we believe that we will be able to deliver more and new products over the next decade."

1. *WHO Global Centre for Traditional Medicine, 2022*

For more information please visit plantacorp.com

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advanced liposomal technology

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we could see...

£68bn

in GDP added to the UK economy

from increased investment in cutting-edge R&D.

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